Statistical Analysis Plan

Protocol Number: MT-6345-E01

A Randomised, Double-Blind, Placebo-Controlled Phase I Study to Investigate the Safety, Tolerability and Pharmacokinetics of Single and Multiple Ascending Doses of MT-6345 in Healthy Subjects; Including Investigation of the Effect of Food, Gender and Race on the Pharmacokinetics of a Single Dose of MT-6345 in Healthy Subjects

Version: v1.0
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Prepared By:	Mitsubishi Tanabe Pharma Corporation
Version:	v1.0
Date:	1JUL2020

APPROVAL FORM

Statistical Analysis Plan

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Approval date:	

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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
ALT	alanine transaminase
BDRM	blinded data review meeting
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
DP	decimal places
ECG	electrocardiogram
LLOQ	lower limit of quantitation
MedDRA	medical dictionary for regulatory activities
PK	pharmacokinetics
PKPOP	PK Population (PK analysis set)
PT	preferred term
RAND	all subjects randomized population
SAP	statistical analysis plan
SAE	serious adverse event
SAF	safety population
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse events
ULN	upper limit of normal range
WHO	World Health Organization

LIST OF PK PARAMETERS

Parameters	Unit	Definitions
Ae	mg	Urinary excretion amount of drug
Ae%	%	Urinary excretion ratio of drug
AR	-	Accumulation ratio
AUC_{0-t}	ng·h/mL	Area under the plasma concentration-time curve from zero up to t hour
AUC_{0-last}	ng·h/mL	Area under the plasma concentration-time curve from zero up to the last quantifiable concentration time point
$AUC_{0-\infty}$	ng·h/mL	Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase
$AUC\%_{ex}$	%	Area under the (plasma) concentration-time curve extrapolated from the last quantifiable concentration time point to infinity in % of the total $AUC_{0-\infty}$
C_{max}	ng/mL	Maximum plasma concentration after administration
C_{last}	ng/mL	Last quantifiable concentration
CL/F	L/h	Apparent total clearance
CL_R	L/h	Renal clearance
LF	-	Linearity factor
MRT	h	Mean residence time
$t_{1/2}$	h	Terminal elimination half-life in plasma concentration-time course
V_{ss}/F	L	Apparent volume of distribution at steady state
V_z/F	L	Apparent volume of distribution during terminal phase

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the final protocol (v2.0) dated 12-DEC-2018. The plan covers statistical analysis, tabulations and listings of the study data to investigate the safety, tolerability and pharmacokinetics of single and multiple ascending doses of MT-6345 compared to placebo in healthy subjects.

Any statistical analysis details described in this document supersede any description of statistical analysis in the protocol.

This study was terminated due to brain changes in male rats in the 13-week tox study. Subjects were enrolled in only Part 1, Part 2 and Part 3. Some assessments which were not performed are grayed out in this SAP.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

- To evaluate the safety and tolerability of single and multiple ascending oral doses of MT-6345 administered to healthy subjects.

2.1.2. Secondary Objectives

- To investigate the PK profile of MT-6345 following single and multiple ascending oral doses administered to healthy male subjects.
- To investigate the effect of food and race on the PK profile of MT-6345 following a single oral dose administered to healthy male subjects.
- To investigate the effect of gender on the PK profile of MT-6345 following a single oral dose administered to healthy female subjects.
- To investigate the effect of MT-6345 drug concentration on QT prolongation and QTc interval following single and multiple oral doses administered to healthy subjects.

2.1.3. [redacted]

[redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

Safety assessments

- Incidence and severity of adverse events (AEs).

- Vital signs (supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- ECG parameters (including heart rate and cardiac intervals: PR, QRS, QT and calculation of corrected QT interval using Fridericia's formula [QTcF]).
- Clinical laboratory assessments (including haematology, biochemistry, coagulation and urinalysis).
- Physical examination.
- Part 3 only, in addition: specialist eye examination findings

2.2.2. **Secondary Endpoints**

Pharmacokinetic assessments:

Plasma concentration versus time profile of MT-6345 after single and multiple dosing.

The following PK parameters will be calculated for MT-6345 after single dosing:

- Maximum plasma concentration after administration (C_{max})
- Time to maximum plasma concentration (t_{max}).
- Plasma terminal elimination half-life- ($t_{½}$).
- Area under the plasma concentration-time- curve from time zero to 24 hours ($AUC_{0\text{-}24h}$).
- Area under the plasma concentration-time- curve from time zero to the last measurable concentration ($AUC_{0\text{-}last}$).
- Area under the plasma concentration-time curve from zero up to infinity with extrapolation of the terminal phase ($AUC_{0\text{-}\infty}$)
- Terminal elimination rate constant (Kel).
- Mean residence time (MRT).
- Apparent oral clearance (CL/F).
- Apparent volume of distribution during terminal phase (Vz/F)
- Apparent volume of distribution at steady state (Vss/F)

The following PK parameters will be calculated for MT-6345 after multiple dosing where appropriate:

- C_{max}.
- t_{max}.
- $t_{½}$.
- Area under the plasma concentration-time- curve over the dosing interval ($AUC_{0\text{-}\tau}$).
- $AUC_{0\text{-}last}$.
- $AUC_{0\text{-}\infty}$.
- Kel.
- MRT.
- CL/F.

- Apparent volume of distribution at steady state (V_{ss}/F).
- Apparent volume of distribution during terminal phase (Vz/F)
- Linearity factor (LF).
- Accumulation ratio (AR).
- Urinary excreted amount of test compound (Ae).
- Urinary excreted amount of test compound expressed as a percentage of the dose administered (Ae%).
- Renal clearance (CL_R).

QT interval assessments

Continuous 12-lead Holter data will be obtained from subjects in Parts 1 and 3. Data will be analysed following completion of the study to investigate the potential effect of MT-6345 on QTc interval or stored for future analysis.

2.2.3. [redacted]

3. STUDY DESIGN

This was a Phase I, randomised, double-blind, placebo-controlled, single-centre study, comprising five parts. It was planned to randomise 100 subjects. If required, one additional cohort of 8 subjects and one cohort of 12 subjects may have been added to Parts 1 and 3, respectively.

The study sequences are illustrated in Figure 1 and Figure 2.

3.1.1. Planned Study Design

Part 1: Single ascending dose (SAD)

Up to 48 healthy Caucasian males, aged 18 to 55 years who meet the study criteria will be allocated to six cohorts of 8 subjects each. One additional cohort of 8 male subjects may be enrolled (e.g., in case the mean maximum observed human exposure value at the highest dose is at least 50% lower [i.e., 22,625 ng.h/mL] than the AUC at the NOAEL in rat [45,250 ng.h/mL]). In each cohort, 6 subjects will be randomised to receive a single dose of MT-6345 and 2 subjects will be randomised to receive a matching dose of placebo.

All cohorts will have 2 sentinel subjects of whom 1 subject will receive MT-6345 and 1 subject

will receive matched placebo. The remaining 6 subjects, of whom 5 subjects will receive MT-6345 and 1 subject will receive placebo, will be dosed at least 24 hours following the sentinel subjects.

The dose levels are planned to be administered in ascending order. Subjects will receive a single dose of MT-6345 or placebo in a fasted state (for at least 10 hours). Progression to the next dose level, and dose selection, will be based on all available safety and tolerability data up to at least 48 hours post-dose and available PK data (up to at least 24 hours post-dose) from a minimum of 6 subjects (MT-6345 n≥4) in the preceding dose cohort.

The dose administered to Cohort 1 will be [redacted] The anticipated dosing schedule is [redacted] and [redacted] The maximum dose in Part 1 (SAD) is anticipated to be [redacted] however, this will be selected based upon emerging PK, safety and tolerability data from previous cohorts, but will not exceed an individual exposure limit of 45,250 ng.h/mL (AUC_{0-24h}).

The maximum number of capsules which are planned to be administered in this group are up to 24 x [redacted] capsules (size 3) of MT-6345 or matching placebo, in the [redacted] cohort. MTPE has experience with a first-in-man study (MT-3995-E01, EudraCT: 2009-014884-38) where the SAD part of the study required the administration of 32 x size 3 capsules (diameter 5.82 mm) at the highest dose level. This dose level was administered with no significant impact on the subjects or study. Subjects will be permitted additional water to help swallow the capsules if necessary. At Screening all subjects will be questioned on whether they have any known history of difficulty in swallowing a large size or number of capsules. Any subject with such a history will be excluded from the study as per exclusion criterion 24.

Continuous 12-lead Holter data will be obtained from subjects in Part 1. Data will be analysed following completion of the study to investigate the potential effect of MT-6345 on QTc interval or stored for future analysis.

Part 2: Food effect

A single cohort from Part 1 (anticipated to be Cohort 3; [redacted] MT-6345) will be selected to return for a second treatment period to investigate the effect of food (after a Food & Drug Administration [FDA]-approved high-fat breakfast)[14] on the PK of MT-6345. There will be a minimum of 15 days between the last dose administration in Part 1 and the first dose administration in Part 2. Subjects in Part 2 will receive the same dose (active or placebo) that they received in Part 1.

The dose and cohort selected for Part 2 will not be confirmed until safety, tolerability and PK data from the intended dose level in Part 1 has been reviewed and deemed acceptable. The intention is for all 8 subjects to be dosed sequentially on the same day.

Part 3: Multiple ascending dose (MAD)

A total of 36 healthy Caucasian males, aged 18 to 55 years, who meet the study eligibility criteria, will be allocated to three cohorts of 12 subjects each. An additional cohort of 12 healthy male subjects may be enrolled (e.g., in case the mean maximum observed human exposure value at the highest dose is at least 50% lower than the AUC at the NOAEL in rat [22,625 ng.h/mL]). In each cohort, 9 subjects will be randomised to receive multiple doses of MT-6345 and 3 subjects will be randomised to receive matching doses of placebo.

The current dosing regimen in Part 3 is anticipated to be 14 days multiple-dose administration of MT-6345 or placebo capsules once daily on Days 1 to 14. The duration of dosing may be altered based upon emerging PK data but will not exceed 28 days.

The MAD cohorts may consist of sentinel dosing (1 subject will receive MT-6345 and 1 subject will receive matched placebo). Whether sentinel cohorts are needed will be decided based upon review of prior SAD and MAD cohorts. The remaining 10 subjects, of whom 8 subjects will receive MT-6345 and 2 subjects will receive placebo, will be dosed when the first MT-6345 dosed sentinel subject is predicted to have reached steady state concentration of MT-6345 (five half-lives).

The dose levels are planned to be administered in ascending order. Progression to the next dose level, and dose selection, will be based on the safety, tolerability and available PK data from Part 1 and the preceding dose cohort in Part 3 (safety and tolerability data up to 72 hours after the last dose and available PK data up to 24 hours after the last dose, from a minimum of 10 subjects [MT-6345 n≥7] in the preceding dose cohort).

The anticipated doses are [redacted] and [redacted] once daily; however, the choice of doses will be reviewed and may be altered based on the emerging data.

Continuous 12-lead Holter data will be obtained from subjects in Part 3. Data will be analysed following completion of the study to investigate the potential effect of MT-6345 on QTc interval or stored for future analysis.

In Part 3, subjects will be admitted to the [redacted] 2 days prior to the first dosing (evening of Day -2). The first dose of MT-6345 or placebo will be administered on the morning of Day 1. Subjects will remain in the [redacted] until 72 hours post-dose after the final dose. Subjects will return for outpatient visits (if the subjects are not confined to the [redacted]) and PK blood samples will be taken at 5 and 8 days after last dosing. Subjects will return to the [redacted] 14 days after last dosing for a Follow-up Visit.

Part 4: Gender effect

One cohort of eight healthy Caucasian females, aged 18 to 55 years, who meet the study

eligibility criteria, will be investigated to determine the effect of gender on PK following a single oral dose of MT-6345. The anticipated dose is [redacted] however, this may be modified based on emerging PK, safety and tolerability data from Part 1. The dose selected will not be confirmed nor administered until safety, tolerability and PK data from the intended dose level in Part 1 has been reviewed and deemed acceptable. Subjects will be randomised (MT-6345, n=6: placebo, n=2) to receive a single dose of MT-6345 or placebo in a fasted state (for at least 10 hours).

Part 5: Race effect – Japanese

One cohort of eight healthy Japanese males, aged 18 to 55 years, who meet the study eligibility criteria, will be investigated to determine the effect of race on PK following a single oral dose of MT-6345. The anticipated dose is [redacted] however, this may be modified based on emerging PK, safety and tolerability data from Part 1. The dose selected will not be confirmed nor administered until safety, tolerability and PK data from the intended dose level in Part 1 has been reviewed and deemed acceptable. Subjects will be randomised (MT-6345, n=6: placebo, n=2) to receive a single dose of MT-6345 or placebo in a fasted state (for at least 10 hours).
Subjects in Part 1 will be admitted to the [redacted] 2 days prior to dosing (evening of Day -2) in order to begin Holter Monitoring on Day -1 and [redacted].
Subjects in Parts 2, 4 and 5 will be admitted to the [redacted] 1 day prior to dosing (Day -1). MT-6345 or placebo will be administered on the morning of Day 1. Subjects in Parts 1, 2 and 4 will remain in the [redacted] until 48 hours post-dose, i.e., the morning of Day 3. Subjects will return for outpatient visits and PK blood samples will be taken at Day 4, Day 6 and Day 9. Japanese subjects in Part 5 will remain in the [redacted] until 120 hours post-dose, i.e., the morning of Day 6.
Subjects will return to the [redacted] on Day 15 for a Follow-up Visit.
The same dose will be used for each cohort in Parts 2, 4 and 5.

Figure 1 Study design scheme for Parts 1, 2, 4 and 5

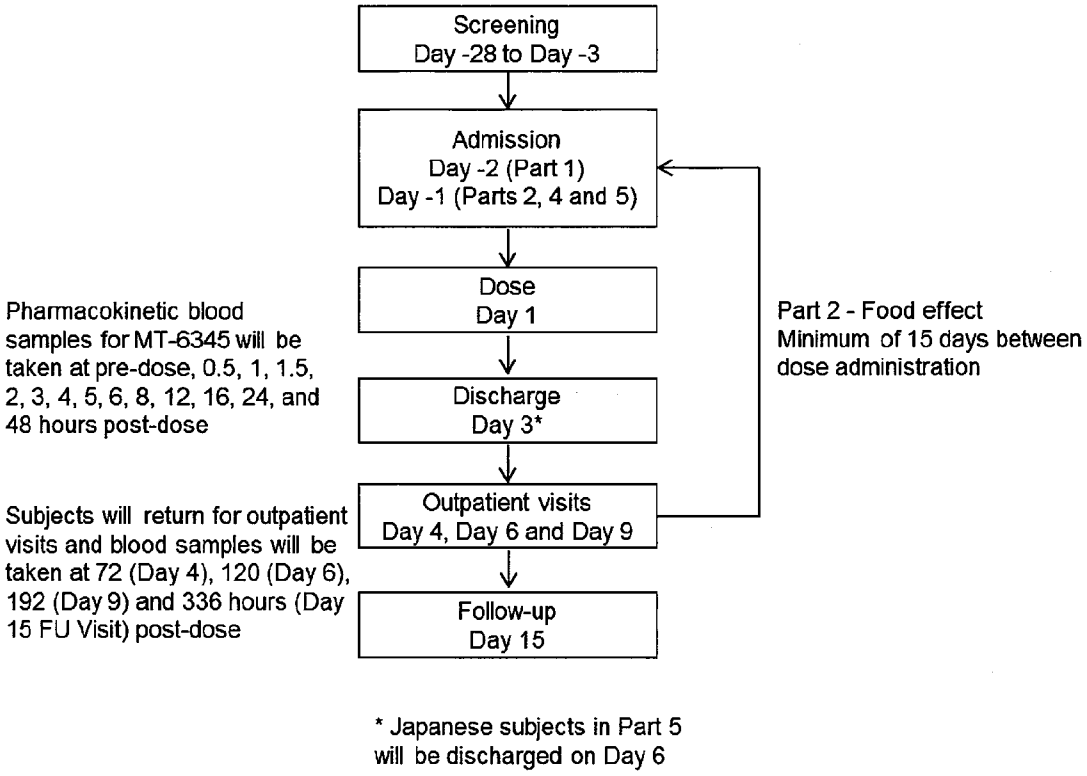
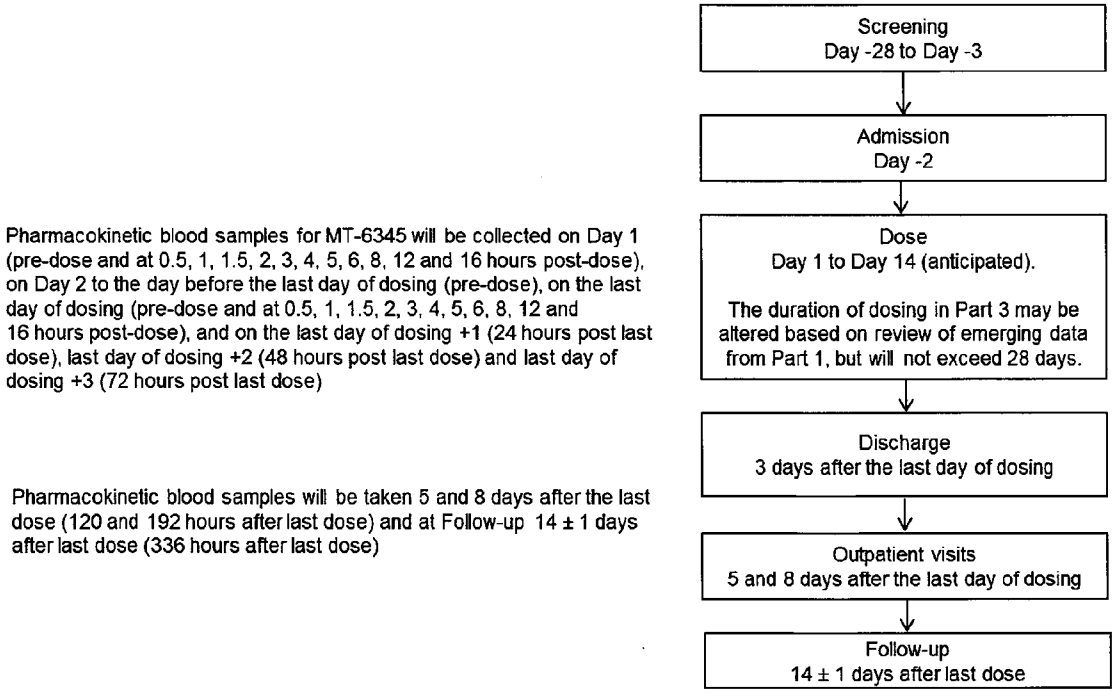


Figure 2 Study design scheme for Part 3



3.1.2. Actual Study Outcome

This study was terminated due to brain changes in male rats in the 13-week tox study. Subjects were enrolled in only Part 1, Part 2 and Part 3. Along with this, some assessments were not performed in these parts and they are grayed out in this SAP.

3.2. Schedule of Study Procedures

Study assessments are summarised in the time and events schedule (Table 1, 2 and 3).

Table 1 Time and events schedule for Parts 1, 2*, 4 and 5

Study Day	SCR	ADM	Treatment day																	FU
	-28 to -3/-2	-2/-1	1													2	3	4	6	15 ± 1
Time point hours)			Pre	0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72	120	192	
Confinement[1]		<----------															---------->				
Outpatient	X																	X	X	X	X
Randomisation			X																		
IMP administration				X																	
Informed consent	X																				
Demography and medical history	X																				
Inclusion/exclusion criteria	X	X	X																		
Body weight and BMI	X	X																			X
Height	X																				
Drug and alcohol screening[2]	X	X																			
Serology[3]	X																				
Pregnancy test[4]	X	X																			X
FSH blood test[5]	X																				
Physical examination[6]	X																				X
Eye examination	X																				X
Supine blood pressure, pulse and respiratory rate	X	X	X			X		X		X			X	X		X	X				X
Oral body temperature	X	X	X			X		X		X			X	X		X	X				X
12-lead Holter ECG[7]		<----------															---------->				
12-lead ECG (standard safety)[8]	X	X	X			X		X	X				X			X					X

Study Day	SCR	ADM	Treatment day																		FU
	-28 to -3/-2	-2/-1	1													2	3	4	6	9	15 ± 1
Time point hours)			Pre	0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72	120	192	
Haematology, biochemistry, coagulation and urinalysis	X	X														X	X				X
Blood sampling for PK[9]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]			[redacted]			[redacted]	[redacted]	[redacted]		[redacted]	[redacted]						[redacted]				
			[redacted]				[redacted]										[redacted]				
			[redacted]														[redacted]				
Adverse events	<----------																				---------->
Concomitant medications	<----------																				---------->

Abbreviations: ADM=admission; BMI=body mass index; ECG=electrocardiogram; FSH=follicle stimulating hormone; FU=Follow-up Visit; HIV=human immunodeficiency virus; IMP=Investigational Medicinal Product; [redacted] PK=pharmacokinetic; [redacted] QTcF=corrected QT interval using Fridericia's formula; SCR=Screening Visit.

1. Subjects admitted on the evening of Day -2 for Part 1, and the morning of Day -1 for Parts 2, 4 and 5. Subjects will be discharged on the morning of Day 3 with the exception of Japanese subjects in Part 5 who will be discharged the morning of Day 5.
2. Urine drugs of abuse screen will include tests for methadone, cocaine, tetrahydrocannabinol, benzodiazepines, barbiturates, amphetamines and opiates. Carbon monoxide and alcohol breath tests will also be performed.
3. Serology testing for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibodies and HIV 1/2 antibodies.
4. Female subjects only. Part 1, A serum pregnancy test will be performed at Screening and a urine pregnancy test at all other time points.
5. Samples only Part 4. The sample taken for biochemistry analysis will be used to measure FSH.
6. A full physical examination will be performed at Screening and Day 15 FU. At other times, a targeted (symptom driven) physical examination of relevant body system(s) will be performed following physician assessment if the subject reports feeling unwell or an adverse event.
7. Continuous 12-lead Holter data will be obtained from subjects in Part 1. Continuous ECG will be collected from approximately 24 hours prior to dosing (Day -1) to 24 hours post-dosing (Day 2). Electrocardiogram extractions will occur at each PK blood sampling time point during this period.
8. A 12-lead ECG (heart rate and cardiac intervals: PR, QRS, QT and QTcF) will be performed at Day -1 (-0.5, 1, 2, 3, 8) and Day 1 (pre-dose, 1, 2, 3, 8 hours post-dose) and Day 2 (24 hours post-dose).
9. PK blood samples for MT-6345 will be taken at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, and 48 hours post-dose. Subjects will return for outpatient visits and PK blood samples will be taken at 72 (Day 4), 120 (Day 6), 192 (Day 9) and 336 hours (Day 15 FU) post-dose.

[redacted]

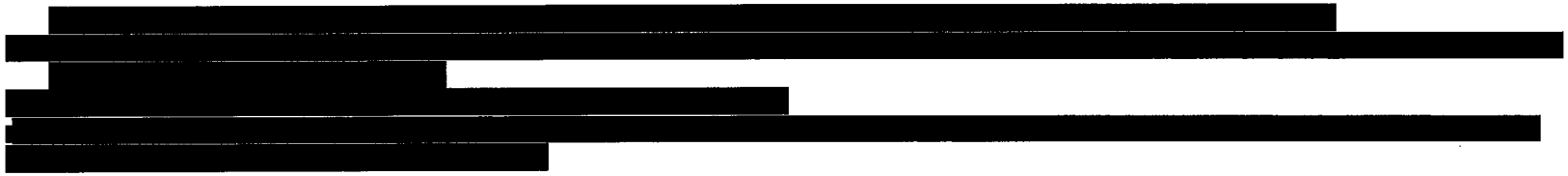


Table 2 Time and events schedule for Part 3

Study Day	SCR	Treatment day		FU
	-28 to -3	Day -2 to maximun of Day 31 (confinement period)	5 and 8 days after last dose	14 ± 1 days after last dose
Outpatient visit	X		X	X
Informed consent	X	Refer to Table 3 Time and events schedule for Part 3 (confinement period) for confinement period assessments		
Demography and medical history	X			
Inclusion/exclusion criteria	X			
Body weight and BMI	X			X
Height	X			
Drug and alcohol screening[1]	X			
Serology[2]	X			
Physical examination[3]	X			X
Eye examination[4]	X			X
Supine blood pressure, pulse and respiratory rate	X			X
Oral body temperature	X			X
12-lead ECG (safety)	X			X
Haematology, biochemistry, coagulation and urinalysis	X			X
Blood sampling for PK[5]			X	X
[redacted]				[redacted]
Adverse events	<----------	----------	----------	---------->
Concomitant medication	<----------	----------	----------	---------->

Abbreviations: BMI=body mass index; ECG=electrocardiogram; [redacted]; FU=Follow-up Visit; HIV=human immunodeficiency virus; PK=pharmacokinetic; SCR=Screening Visit.

1. Urine drugs of abuse screen will include tests for methadone, cocaine, tetrahydrocannabinol, benzodiazepines, barbiturates, amphetamines and opiates. Carbon monoxide and alcohol breath tests will also be performed.
2. Serology testing for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibodies and HIV 1/2 antibodies.
3. Full physical examination will be performed at Screening and Follow-up. At other times, a targeted (symptom driven) physical examination of relevant body system(s) will be performed following physician assessment if the subject reports feeling unwell or an adverse event.
4. Conducted by a Consultant Ophthalmologist. Further details can be found in Section 6.5.1. Screening examination may be performed at any time between Day -28 and Day -3. Follow-up examination may be performed at any time between last dosing and the Follow-up Visit.
5. PK blood samples for MT-6345 will be collected during the confinement period (see Table 3). Subjects will return for outpatient visits and PK blood samples will be taken 5 and 8 days after the last dose (120 and 192 hours after last dose), and at FU 14 ± 1 days after last dose (336 hours after last dose).

[redacted]

Table 3 Time and events schedule for Part 3 (confinement period)

Study Day	ADM	Treatment day																														
	-1	1													2	3	4	5	6	7	MDD[1]	8	9	10	11	12	13 to LDD -1[1]	LDD[1]	LDD +1	LDD +2	LDD +3
Time point (hours)		Pre	0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72	96	120													
Confinement[4]	<----------																															
Randomisation		X																														
IMP administration			X												X	X	X	X	X	X		X	X	X	X	X	X	X				
Inclusion/ exclusion criteria	X	X																														
Body weight and BMI	X																					X						X			X
Eye Examination[5]																					X											
Drug and alcohol screening[6]	X																															
Supine blood pressure, pulse and respiratory rate[7]	X	X			X		X		X			X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Oral body temperature	X	X			X		X		X			X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
12-lead Holter ECGs[8]	<----->																											<--->				
12-lead ECG (safety)[9]	X	X			X		X	X				X			X	X	X	X	X	X		X	X	X	X	X	X	X	X		X
Haematology, biochemistry, coagulation and urinalysis[10]	X														X	X		X				X							X		X
[redacted]	■																			■				■				■			

Study Day	ADM	Treatment day																														
	-1	1													2	3	4	5	6	7	MDD[1]	8	9	10	11	12	13 to LDD -1[1]	LDD[1]	LDD +1	LDD +2	LDD +3
Time point (hours)		Pre	0	0.5	1	1.5	2	3	4	5	6	8	12	16	24	48	72	96	120													
Blood sampling for PK[11]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
[redacted]		[redacted]				[redacted]		[redacted]			[redacted]		[redacted]		[redacted]													[redacted]	[redacted]	[redacted]	[redacted]
Urine sampling for PK[13]		<----------													>													<-->			
[redacted]		<----------													>													<-->			
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]		[redacted]																			[redacted]			[redacted]
[redacted]		[redacted]																				[redacted]						[redacted]			[redacted]
[redacted]		[redacted]																										[redacted]			
Adverse events	<----------																															
Concomitant medication	<----------																															

Abbreviations: ADM=admission; BMI=body mass index; ECG=electrocardiogram; [redacted] IMP=Investigational Medicinal Product; LDD=last day of dosing; MDD=midpoint dosing day; [redacted]
PK=pharmacokinetic; [redacted] QTcF=corrected QT interval using Fridericia's formula.

1. e.g. if duration of dosing is 14 days then should be on Day 7 (+/- 2 days)
2. Subjects will receive a once daily dose of MT-6345 for at least 14 days. Dosing can be extended out as far as Day 28, so the day before the LDD can be Day 13 up to a maximum of Day 27.
3. The LDD will be Day 14, at a minimum. Dosing can be extended out as far as Day 28.
4. Subjects admitted on the evening of Day -2; assessments will be performed on Day -1. Subjects will be discharged 72 hours after the LDD (Day 17 at minimum, Day 31 at maximum).
5. Conducted by a Consultant Ophthalmologist. Further details can be found in Section 6.5.1
6. Urine drugs of abuse screen will include tests for methadone, cocaine, tetrahydrocannabinol,benzodiazepines, barbiturates, amphetamines and opiates. Carbon monoxide and alcohol breath tests will also be performed.
7. Vital sign assessments to be conducted at pre-dose on Day 2 to the LDD.
8. Continuous ECG will be collected from approximately 24 hours prior to dosing on Day -1 until pre-dosing on Day1; and from pre-dose on the LDD to 24 hours after last dosing (LDD +1). ECG extractions to occur at each PK blood sampling time point during this period.
9. A 12-lead ECG (heart rate and cardiac intervals: PR,QRS, QT and QTcF) will be performed at Day -1 (-0.5,1, 2,3 and 8 hours relative to expected dose time on Day 1); Days 1, 8 and LDD (at pre-dose,1, 2, 3 and 8 hours post-dose); Days 2 to 7 (pre-dose); Days 9 to the day before the LDD (pre-dose); and 24 hours and 72 hours after the LDD(LDD +1and LDD +3).
10. If dosing is extended beyond 14 days, a blood sample will be taken on Day 14 and every 7 days thereafter.
11. PK blood samples for MT-6345 will be collected on Day1 (pre-dose and at 0.5,1, 1.5, 2, 3, 4, 5, 6, 8,12 and 16 hours post-dose), Day 2 to LDD -1 (pre-dose), LDD (pre-dose and at 0.5,1, 1.5, 2, 3, 4, 5, 6, 8,12 and 16 hours post-dose), and on LDD +1 (24 hours post last dose), LDD +2 (48 hours post last dose) and LDD +3 (72 hours post last dose).

[redacted]

13. PK urine samples for MT-6345 will be collected at Day-1 (-24 hours 0 hours), Day1 (0 hours to 24 hours) and LDD(0 hours to 24 hours).

[redacted]

3.3. Sample Size and Power Considerations

3.3.1. Planned Sample Size and Power Considerations

It is planned to enrol up to 100 subjects in this study, which may be extended to 120 subjects if additional cohorts are included in Parts 1 and 3 of the study:

Part 1: 48 healthy male Caucasian subjects allocated to one of six dose cohorts comprising 8 subjects each. An additional cohort of 8 subjects may be enrolled.

Part 2: 8 healthy male Caucasian subjects (cohort selected from Part 1).

Part 3: 36 healthy male Caucasian subjects allocated to one of three dose cohorts comprising 12 subjects each. An additional cohort of 12 subjects may be enrolled.

Part 4: 8 healthy female Caucasian subjects.

Part 5: 8 healthy male Japanese subjects.

There are 8 subjects in each cohort from Parts 1, 4 and 5, and 12 subjects in each cohort from Part 3 (randomised in a 3:1 ratio to MT-6345:placebo). All cohorts in Part 1 will include 2 sentinel subjects dosed on the first dosing day, of whom one will receive active drug and one will receive placebo. The MAD cohorts may consist of sentinel dosing (1 subject will receive MT-6345 and 1 subject will receive matched placebo). Whether sentinel cohorts are needed will be decided based on review of prior SAD and MAD cohorts. The remaining 10 subjects, of whom 8 subjects will receive MT-6345 and 2 subjects will receive placebo, will be dosed when the first MT-6345 dosed sentinel subject is predicted to have reached steady state concentration of MT-6345 (five half-lives).

The sample size is not based on a formal statistical evaluation but was considered to be adequate to meet the objectives of the study and is a typical size for first-in-man SAD and MAD studies. A sufficient number of subjects will be screened to ensure that the planned sample size will be achieved.

3.3.2. Actual Sample Size

This study was terminated due to brain changes in male rats in the 13-week tox study. Subjects were enrolled in only Part 1, Part 2 and Part 3. 52 subjects were actually randomized as follows.

Part 1: 44 subjects in total; 8 subjects for [redacted] and [redacted] cohorts respectively, and 6 subjects for [redacted] and [redacted] cohorts, respectively.

Part 2: 6 subejcts returned to received the same [redacted] dose as in Part 1 (active or placebo), are therefore not unique patients and are not counted again in the total number of exposed subjects.

Part 3: 8 subjects in the [redacted] cohort

4. PLANNED ANALYSIS

This SAP will be finalized before database lock. Final data analysis will be conducted after database lock.

5. ANALYSIS POPULATIONS

Analysis Population	Definition
Randomised Population (RAND)	All subjects randomised.
Safety analysis set (SAF)	All randomized subjects who received at least one dose of IMP.
PK analysis set (PKPOP)	All subjects who complete the study without having a major emesis episode within 2 hours of dosing on that day and have evaluable PK parameters. The PK data from subjects with emesis within 2 hours of dosing may be analysed separately.

The SAF or RAND will be used for study population-related evaluations. The SAF will be used for all safety evaluations. The PKPOP will be used for the PK analyses.

6. STATISTICAL CONSIDERATIONS

6.1. Descriptive Statistics

(1) Non-PK related

Continuous data will be summarized descriptively using the number in the analysis set (N), the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. Categorical data will be summarized using frequency counts and percentages. The denominator for the percentages will be the total number of subjects in the treatment group and analysis population being presented, unless otherwise specified.

For numerical variables, change from baseline will be calculated as the post-baseline value minus the baseline value. If percentage change from baseline is required, then percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100. If baseline value cannot be determined for a particular variable, the change from baseline and percentage change from baseline will not be calculated.

Unscheduled visits will not be displayed in by-visit summary tables, but will be included in the data listings.

All data will be listed. Listings will include treatment, scheduled, unscheduled, retest and early

discontinuation data. No visit windowing will be performed for this study.

(2) PK related

Plasma concentrations will be summarized descriptively using N, n, mean, SD, median, minimum and maximum.

The plasma and urine PK parameters will be summarized descriptively using N, n, arithmetic mean, SD, median, minimum, maximum, CV%, geometric mean and geometric CV%

CV% and Geometric CV% will be calculated as follows:

$$\text{CV\%} = \frac{\text{standard deviation}}{\text{arithmetic mean}} \times 100$$

$$\text{Geometric CV\%} = \sqrt{[\exp(\sigma^2) - 1]} \times 100$$

where σ represents the standard deviation computed on the natural logarithmic transformed concentrations.

6.2. Statistical Tests

Not Applicable for this study.

7. DATA CONVENTIONS

7.1. Analysis Variable Definitions

7.1.1. Study Subjects

7.1.1.1. Protocol Deviations

Protocol deviations will be identified and documented during a data review prior to database lock and confirmed by database lock. Major protocol deviations will be defined as deviations that may significantly impact the completeness, integrity, accuracy, and/or reliability of the study data and may significantly affect a subject's rights, safety, or well-being.

7.1.1.2. Demographic and Other Baseline Characteristics

(1) BMI

BMI will be recalculated using the formula below and reported to 1dp.

BMI (kg/m^2) = weight at screening (kg) / {height at screening (m)}^{2}

7.1.1.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or later.

7.1.1.4. Prior or Concomitant Medication

Medications will be coded according to the World Health Organisation Drug Dictionary (WHO-DD) SEP 2017 version.

(1) Prior Medication

Medication taken within 2 weeks of Screening will be recorded in the subject's source documents as prior medication.

(2) Concomitant Medication

Concomitant medication is defined as any medication, other than the IMP, which is taken during the study, including prescription, herbal and over the counter medications.

7.1.2. Safety Assessments

7.1.2.1. Adverse Events

Adverse events will be coded according to the MedDRA version 20.0 or later.

(1) Treatment Emergent Adverse Events/ Treatment Emergent Serious Adverse Events (TEAEs/TESAEs)

AEs/SAEs will be classified as 'treatment-emergent' if they arise following the first administration of IMP or if a pre-dose AE increases in severity following dosing.

(2) Adverse Drug Reaction

A TEAE is considered an "adverse drug reaction" if it has been assessed as having a "reasonable possibility" in relationship to the study drug.

(3) Duration of Adverse Events

Duration of Adverse Events (days) = AE stop date – AE start date + 1

7.1.2.2. Laboratory Tests

(1) Laboratory values below the limit of quantification

1/2 LLOQ will be used for BLQ (below the limit of quantification) data in summary statistics.

7.1.2.3. 12-Lead ECG

(1) Criteria for pre-defined limit

12-lead ECG:

- **QTcF : > 450 msec, QTcF > 480 msec, QTcF > 500 msec**
- **Increase from baseline in QTcF : > 30 msec, > 60 msec**

7.1.3. Pharmacokinetics Evaluation

7.1.3.1. Plasma Concentration

For the calculation of the summary statistics, concentration values reported as below the limit of quantification (BLQ) will be set to 0. Only valid PK data will be included in the summary tables or figures.

7.1.3.2. Pharmacokinetic Parameters

For the calculation of PK parameters, actual sampling time (in hours rounded to 2 decimal places) relative to dosing should be used. Concentration below the limit of quantification (BLQ) will be imputed with a value of 0. For calculation of AUCs, missing data will be treated as if the respective sample never had been scheduled for the calculation by the linear-linear trapezoidal rule.

For Ae, Ae% and CL_R, geometric mean and geometric CV% will be calculated only when all the individual Ae, Ae% and CL_R is greater than 0 at each sampling time point.

7.1.4. Other Evaluations

For the steady state evaluation, in the case where the trough concentrations for either numerator or denominator is BLQ, the ratio will not be calculated for that day (in this case the result will be shown as not calculated [NC] in the listings and will be excluded from the summary statistics).

7.2 Analysis Visit Definitions

(1) Non-PK related

No visit windowing will be performed for this study.

Unless otherwise specified, baseline will be the last observed value of the parameter of interest prior to the first intake of study drug (this includes unscheduled visits). For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If the distance to the nominal day is the same, the data of later date will be used.

(2) PK related

The analysis visit window will be the following.

For Part 1 and 2

Analysis visit	Nominal time(hour)	Window
Pre dose	0	-60 min to 0
Day 1 0.5H – 1.5H	0.5 - 1.5	within ± 5 min
Day 1 2H – 3H	2 - 3	within ± 15 min
Day 1 4H - 6H	4 - 6	within ± 30 min
Day 1 8H - 16H	8 - 16	within ± 3 hour
Day 2	24	within ± 3 hours
Day 3	48	within ± 6 hours
Day 4	72	within ± 12 hours
Day 6	120	within ± 18 hours
Day 9 - Follow up	192 - 336	within ± 24 hours

For Part 3 except for urine PK

Analysis visit	Nominal time(hour)	Window
Pre dose	0	-60 min to 0
Day 1 0.5H – 1.5H	0.5 - 1.5	within ± 5 min
Day 1 2H – 3H	2 - 3	within ± 15 min
Day 1 4H – 6H	4 - 6	within ± 30 min
Day 1 8H – 16H	8 - 16	within ± 1 hour
Day 2 to LDD-1		within ± 3 hour
LDD 0.5H – 1.5H	0.5 - 1.5	within ± 5 min
LDD 2H – 3H	2 - 3	within ± 15 min
LDD 4H – 6H	4 - 6	within ± 30 min
LDD 8H – 16H	8 - 16	within ± 1 hours
LDD +1		within ± 6 hours
LDD +2		within ± 6 hours
5 days after last dose		within ± 12 hours
8 days after last dose		within ± 24 hours
Follow up	Day 15	within ± 24 hours

The analysis visit window for Urine PK is within the following time after the nominal time; -30 to +30 minutes.

7.3 Data Handling Convention for Missing Data

(1) **Non-PK related**

Adverse events:

If severity or relationship is found to be missing, the most severe occurrence will be imputed for the summary of interest.

For missing or partial AE start dates, the AE will be treated as a TEAE if it cannot be determined to be a non-TEAE. Adverse events with unknown start and/or end times (but where the date is known) will be imputed with a time of 23.59 h for the tabulations but will be shown as NK:NK in the listings (where NK = Not Known)

Other Safety-related endpoints:

For other safety-related summaries, only observed data will be used. Unless otherwise specified, missing safety data will not be imputed.

(2) **PK related**

For PK summaries, only observed data will be used. Missing PK data will not be imputed. When calculating Ae and Ae%, missing PK data will be imputed to 0.

7.4 Handling of data for PK assessments

PK data that are considered "invalid" will be flagged in the listing. The PK data handling was assessed during BDRM prior to database lock and in the investigation of PK data handling assessment after unblinding. A separate PK data handling document will be produced to cover both pre- and post- unblinding decisions.

If PK sample handling errors or other factors are identified after data unblinding and these errors have led to unexpected erroneous data, then these erroneous data will be regarded as "invalid".

8 STATISTICAL METHODOLOGY

8.1 Study Subjects

8.1.1 Subject Disposition

Subjects' disposition will be summarized for all the subjects. Subjects who discontinued will be summarized by reasons for discontinuation.

Randomization details and subject disposition will be listed for RAND. Screen failures and inclusion and exclusion criteria deviation at screening will be listed for All Subjects.

8.1.2 Analysis Populations

Analysis populations will be summarized and listed for RAND.

8.1.3 Protocol Deviations

Protocol Deviations will be listed for RAND.

8.1.4 Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Category	**Descriptive**
Sex	Male, Female	
Age (years)		Yes
Height (cm)		Yes
Weight (kg)		Yes
BMI (kg/m^2)		Yes
Race	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other	
Ethnicity	Not Hispanic or Latino, Hispanic or Latino, Unknown	

Demographic and other baseline characteristics will be summarized for the SAF by study part and treatment.

Demographic data will be listed for the SAF and other baseline characteristics (including alcohol consumption) will be listed for the SAF for each part of the study.

8.1.5 Medical History

Medical history data will be listed for the RAND.

8.1.6 Prior or Concomitant Medications

Prior and concomitant medication will be listed for the RAND.

8.1.7 Study Drug Administration

For Part 3, study drug administration will be listed for RAND.

8.2 Safety Assessments

Safety assessments will be made for the SAF. All safety data will be listed.

8.2.1 Adverse Events

An overall summary including the following will be presented by study part.

- Subjects with at least one TEAE
- Subjects with at least one TESAE
- Subjects with at least one adverse drug reaction
- Subjects with at least one TEAE leading to discontinuation of study drug

The following summaries also will be conducted.

- TEAEs by SOC and PT
- TEAEs by SOC, PT and relationship to study drug

Each of the summaries will be done at the subject level - multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility). If intensity or relationship is found to be missing, the most severe occurrence will be imputed for that particular summary.

All AEs will be listed.

The above TEAE summaries will be produced for each dose level and placebo. For Part 2, all TEAEs will be tabulated in incidence tables by treatment (MT-6435 or placebo) as described above by fasting status. For subjects in Part 2, any AEs occurring in the first (fasting) period during Part 1 will be assigned to Part 1 until the time of dosing in Part 2. Therefore any AEs that occur during the washout period will be assigned to Part 1.

8.2.2 Laboratory Tests

Laboratory test reference ranges will be listed.

Absolute values will be summarized and listed at each timepoint for each study part by dose level and by fed state for the following parameters.

Laboratory Test	Parameters
Haematology	Haemoglobin, Haematocrit, Platelet Count, Red Blood Cell Count, Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), White Blood Cell Count and Differential
Biochemistry	Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Gamma-glutamyl transpeptidase, Potassium, Sodium, Chloride, Inorganic phosphate, Glucose, Urea, Bilirubin (direct and total), Cholesterol, Triglycerides, High density lipoprotein-cholesterol, Low density lipoprotein-cholesterol, Protein (total), Albumin, Creatine kinase, Creatinine, Follicile stimulating hormone (FSH)[1], Human Chorionic gonadotrophin (hCG)[2]
Coagulation	Prothrombin time, International normalised ratio, Activated partial thromboplastin time
Urinalysis	Specific gravity, pH, Protein, Glucose, Ketones, Urobilinogen, Blood, Human chorionic gonadotropin (hCG)[2], Microscopic examination[3]

[1] Females only; performed at Screening only

[2] Females only; a serum pregnancy test will be performed at Screening and a urine pregnancy test at all other time points

[3] Performed only if required, based on urinalysis results

8.2.3 Vital Signs

Absolute values will be summarized and presented at each timepoint for each study part by dose level and by fed state for the following parameters.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breath/min)
- Oral Body Temperature (°C)
- Overall evaluation

All data will be listed.

8.2.4 12-Lead ECGs

Absolute values will be summarized and presented at each timepoint for each study part by dose level and by fed state will for the following parameters.

- PR (msec)

- QRS (msec)
- QT (msec)
- QTcF (msec)
- Overall evaluation

The frequency counts and percentages of subjects with 12-lead ECG values outside pre-defined limits will be summarized

All data will be listed.

8.2.5 Physical Examinations

Physical examination body systems examined at Screening and Follow-up will be

- Head
- Ears/Nose/Throat
- Abdominal
- Cardiovascular
- Respiratory
- Dermatological
- Musculoskeletal
- Neurological
- Eyes
- General appearance
- Neck
- Lymph Nodes
- Other

Abbreviated physical Examination body systems examined at all other visits.

All data will be listed.

8.2.6 Eye Examinations

Eye examination data will be listed.

8.3 Pharmacokinetics Evaluation

8.3.1. Plasma and Urine Concentration

Plasma MT-6345 concentrations will be summarized at each nominal sampling point by dose group for single dose group, multiple dose group and food state. All plasma and urine concentrations will also be listed.

Plots for single dose group;
For each dose group and food state, individual plasma concentrations vs. actual time for 0-24hr and 0-t hr (t: last sampling time point) will be plotted on both linear/linear and log/linear scales for MT-6345. Mean plasma concentrations vs. nominal time curves for 0-24hr and 0-t hr will be plotted on both linear/linear (+SD) and log/linear scales overlaid by all dose groups MT-6345. Plots will also be prepared overlaid by food state, as appropriate.

Plots for multiple dose group;
For each dose group, individual plasma concentrations vs. actual time will be plotted on both linear/linear and log/linear scales for MT-6345. Mean plasma concentration vs. nominal time curves will be plotted on both linear/linear (+SD) and log/linear scales overlaid by all dose groups for MT-6345. Plots will also be prepared overlaid, as appropriate.

The following mean plots for MT-6345 will be produced:

- Day all: plots on linear/linear (+SD) scale and log/linear scales
- Day 1: plots on linear/linear (+SD) scale for 0-24 hr

8.3.2. **Pharmacokinetic Parameters**

The pharmacokinetic parameters listed in Section 2.2 will be calculated for each subject on active dose using a non-compartmental model. The pharmacokinetic parameters will also be listed. The plasma pharmacokinetic parameters will be summarized by each dose group andfed state. The plasma pharmacokinetic parameters will also be listed for each part.
The urinary pharmacokinetic parameters will be summarized for each dose level. The urinary pharmacokinetic parameters will also be listed.

8.3.3. **Dose Proportionality**

Dose proportionality will be assessed by $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} for single dose using a power model. A schematic representation of this is outlined below:

$$AUC_{0-last} \; or \; AUC_{0-\infty} \; or \; C_{max} = e^{\mu} \cdot Dose^{\beta} \cdot e^{\varepsilon}$$

The following linear model will be fitted to the log-transformed parameters of interest:

$$\log_e \left(AUC_{0-las} \; or \; AUC_{0-\infty} \; or \; C_{max} \right) = \mu + \beta \cdot \log_e (Dose) + \varepsilon$$

Where μ and β are the regression intercept and slope coefficients and ε is the error term; assumed to be normally distributed.
The estimate obtained for β is a measure of dose proportionality. Dose proportionality will be

concluded if the 95% CI for β includes the value 1. The parameter estimates and the 95% CIs will be produced.

The evaluation of the model fit will be done by lack-of-fit. In the case where dose-proportionality across all investigated dose groups cannot be established, additional exploratory analysis will be done by either fitting power model on subgroup of investigated dose groups or other data-driven analysis, if deemed appropriate.

To evaluate dose proportionality graphically the following plots will be produced:

- Individual plots of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} versus dose levels on linear and log scales (with the fitted linear regression line for log scales)
- Individual plots for $AUC_{0\text{-last}}$/dose, $AUC_{0\text{-}\infty}$/dose and C_{max}/dose by dose level

8.3.4. **Steady State**

Trough concentrations are the pre-dose concentrations each day (Day 1 to Day X when data is avaiable). The trough concentrations will be listed.

Following plots will be produced:

- Individual trough concentration vs. actual time on linear/linear scale
- Mean trough concentration (+SD) vs. nominal time on linear/linear .

[redacted]

8.4.1. [redacted]

[redacted]

8.4.2. [redacted]

[redacted]

8.4.3. [redacted]

[redacted]

8.4.4. [redacted]

[redacted]

9 DATA PRESENTATION CONVENTIONS

9.1 Number of Digits to Report

(1) **Non-PK related**

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	see section 7.3	All derived data
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages*1	1 DP	All
Ratios	3 DPs	All

*1 Percentages: use 1 DP, except for the following cases:

If the percentage is equal to 0, then leave blank, do not use (0)

If the percentage is equal to 100, then use "(100)" without a decimal

(2) **PK Plasma Concentration**

Statistic	Specification
Individual value, Minimum, Maximum, Mean, SD, Median	4 significant digits

(3) **PK Parameters**

Statistic	Specification
Individual value, Mean, SD, Minimum, Maximum, Median, Geometric mean	C_{max}: the same significant digits as they are reported t_{max}*: 2 DPs $t_{1/2}$: 2DPs Kel; 4DPs Other parameters: 3 significant digits
CV%, Geometric CV%	1 DP

*: t_{max} will be expressed basically in terms of median and range

9.2 Treatments to Report

For Parts 1 (single dose ascending part of study), summaries will be done by dose level with all placebo subjects from each cohort pooled and presented side-by-side with active dose levels. All subjects who received placebo for Part 3 will be pooled into a single placebo group (dose level 0) for the final statistical analysis.

All tables will be sorted by (ascending) dose level, and all active doses will be shown after placebo.

Part 1:

Placebo (N=XX)	MT – 6345 [redacted] (N=XX)	MT – 6345 [redacted] (N=XX)	MT – 6345 [redacted] (N=XX)	MT – 6345 [redacted] (N=XX)	MT – 6345 [redacted] (N=XX)	MT – 6345 [redacted] (N=XX)

Part 2(For Table):

Fed		Fasted	
Placebo (N=XX)	MT - 6345 [redacted] (N=XX)	Placebo (N=XX)	MT - 6345 [redacted] (N=XX)

Part 2(For Listing):

Placebo - Fed/Fasted	MT-6345 [redacted] - Fed/Fasted

Part 3:

Placebo (N=XX)	MT – 6345 [redacted] (N=XX)

9.3 Analysis Visits to Report

(1) Non-PK related

For Part 1 and 2

Analysis Visit	**Apply to**			
	Laboratory Tests	**Vital Signs**	**12-Lead ECG (standard safety)**	**Physical Examinations**
Screening	X	X	X	X
Day -1	X	X	X	
Day 1 / Pre dose		X	X	
Day 1 / 1h		X	X	
Day 1 / 2h		X	X	
Day 1 / 3h			X	
Day 1 / 4h		X		
Day 1 / 8h		X	X	
Day 1 / 12h		X		
Day 2	X	X	X	
Day 3	X	X		
Day 15(FU)	X	X	X	X

For Part 3

Analysis Visit	Apply to			
	Laboratory Tests	**Vital Signs**	**12-Lead ECG (standard safety)**	**Physical Examinations**
Screening	X	X	X	X
Day -1 / Baseline	X	X	X	
Day 1 / Baseline		X	X	
Day 2	X	X	X	
Day 3	X	X	X	
Day 15(FU)	X	X	X	X

Unscheduled visits and retests (same visit number assigned) will not be displayed in by-visit summary tables, but will be included in the data listings.

10 CHANGE FROM THE PROTOCOL

The plaanned analyses below were not done.

- Summary of AEs by SOC, Preferred Term and severity of event
- Summary of the change from baseline for vital signs, 12-lead ECG and routine safety laboratory tests
- A linear mixed model analysis for log-transformed PK parameters
- All analyses for Part 4 or 5

11 SOFTWARE

All statistical analyses will be performed using SAS® version 9.4 or higher.
The PK parameters will be calculated using WinNonlin® software (version 6.3 or later).

12 REFERENCES

N/A

Appendix 1 Pharmacokinetic Parameter Calculations

Actual blood sampling times will be used in the calculation of pharmacokinetic parameters
All concentrations below the LLOQ will be set at zero for pharmacokinetic calculations
When Kel is missing (or cannot be determined), $t_{1/2}$, $AUC_{0-\infty}$, $AUC\%_{ex}$, CL/F, MRT, Vz/F and Vss/F will not be calculated.

PK Parameter Calculations		
Parameters	**Unit**	**Calculation**
C_{max}	ng/mL	will be determined by visual inspection
$AUC_{0-\infty}$	ng·h/mL	$AUC_{0-\infty} = AUC_{0-last} + AUC\%_{ex}$
$AUC\%_{ex}$	ng·h/mL	$AUC_{exp} = C_{last} / Kel$ C_{last}: last measurable concentration
AUC_{0-last}	ng·h/mL	will be calculated using the linear trapezoidal method and actual times $$AUC_{0-la} = \sum_{i=1}^{n} \frac{t_i - t_{i+1}}{2}(C_{i-1} + C_i)$$
t_{max}	h	Measured time of C_{max}
$t_{½}$	h	$t_{½}$ will be determined as: $t_{½} = \log_e(2) / Kel$
Kel	/h	The exponential rate constant of the terminal phase, Kel, will be estimated by log-linear regression, if determinable. The number of data points included in the regression will be determined by visual inspection. Wherever possible, a minimum of 3 data points will be used in the estimation of Kel. During the analysis, this calculation method repeats regressions using the last three points with non-zero concentrations, then the last four points, last five, etc. The time of maximum concentration (tmax) will be excluded from the estimation of Kel. Points with a value of zero for the dependent variable are excluded. For each regression, an adjusted R^2 is computed $$Adjusted\ R^2 = 1 - \frac{(1 - R^2) \times (n - 1)}{(n - 2)}$$

		where n is the number of data points in the regression and R^2 is the square of the correlation coefficient. The regression with the largest adjusted R^2 is selected to estimate Kel, with these caveats: - If the adjusted R^2 does not improve, but is within 0.0001 of the largest adjusted R^2 value, the regression with the larger number of points is used. - Kel must be positive, and calculated from at least three data points.
CL/F	L/h	CL/F = Dose / $AUC_{0-\infty}$
MRT	/h	MRT = $AUMC_{0-\infty}$ / $AUC_{0-\infty}$ $AUMC_{0-\infty}$: area under the first moment curve extrapolated to infinity
Vz/F	L	Vz/F = CL/F x 1/Kel
Vss/F	L	Vss/F = CL/F x MRT
LF	-	LF = $AUC_{0-\tau}$[Day 14]/$AUC_{0-\infty}$[Day 1]
RA	-	RA = $AUC_{0-\tau}$[Day 14]/ $AUC_{0-\tau}$ [Day 1]