Study Protocol

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

Protocol Version and Date: Final v2.0 – 12th December 2018
Incorporating Substantial Protocol Modification 1

NCT number: NCT03809039

Mitsubishi Tanabe Pharma Europe Ltd.

STUDY PROTOCOL

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EudraCT Number:	2018-002478-39
[redacted]	[redacted]
Investigational Medicinal Product:	MT-6345
Development Phase:	Phase I
Sponsor:	Mitsubishi Tanabe Pharma Development America Inc. (MTDA) [redacted]
Sponsor's EU Representative:	Mitsubishi Tanabe Pharma Europe Ltd (MTPE) [redacted]
Sponsor's Responsible Signatory:	[redacted]
Principal Investigator:	[redacted]
Protocol Version and Date:	Final v2.0 – 12th December 2018 Incorporating Substantial Protocol Modification 1

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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

The Protocol has been designed according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice and the Declaration of Helsinki (Fortaleza, Brazil, 2013). It has undergone both medical and scientific review by competent Sponsor personnel.

Sponsor Signatory:
S[redacted]velopment America Inc.

[redacted]

[redacted]
Date

SIGNATURE PAGE (STATISTICIAN)

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

The Protocol has been designed according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice and has undergone statistical review.

[redacted]

[redacted]
Date

SIGNATURE PAGE (PRINCIPAL INVESTIGATOR)

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

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorisation of Mitsubishi Tanabe Pharma Corporation in the form of a Protocol Modification and the appropriate regulatory and Independent Ethics Committee approvals.

Address of Institution:

[redacted]

[redacted]

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADM	Admission
Ae	Urinary excreted amount of test compound
Ae%	Urinary excreted amount of test compound expressed as a percentage of the dose administered
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-24h}	Area under the plasma concentration-time curve from time zero to 24 hours
AUC_{0-last}	Area under the plasma concentration-time curve from time zero to the last measurable concentration
$AUC_{0-\tau}$	Area under the plasma concentration-time curve over the dosing interval
BED	Binge eating disorder
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
CL/F	Apparent oral clearance
CL_R	Renal clearance
C_{max}	Maximum plasma concentration
CS	Clinically significant
CSR	Clinical Study Report
CYP	Cytochrome P450
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
[redacted]	[redacted]
FDA	Food & Drug Administration
FSH	Follicle stimulating hormone
FU	Follow-up Visit
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	Human ether-a-go-go-related gene
HIV	Human immunodeficiency virus
HPF	Highly palatable food
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
Kel	Terminal elimination rate constant
Kp brain	Brain to plasma concentration ratio
LDD	Last day of dosing
LF	Linearity factor
LS	Least square
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRT	Mean residence time

Abbreviation	Definition
MTDA	Mitsubishi Tanabe Pharma Development America
MTPC	Mitsubishi Tanabe Pharma Corporation
MTPE	Mitsubishi Tanabe Pharma Europe Ltd
n	Number of subjects
N	Number of observations
NCS	Not clinically significant
NOAEL	No observed adverse effect level
NR+NS	Non-restricted feeding and not exposed to stress
[redacted]	[redacted]
PDE	Phosphodiesterase
PK	Pharmacokinetic(s)
[redacted]	[redacted]
QA	Quality Assurance
QP	Qualified Person (pharmacist responsible for IMP release at the site)
QTcF	Corrected QT interval using Fridericia's formula
R+S	Restricted feeding and exposed to stress
RA	Ratio of accumulation
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Screening Visit
SD	Standard deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Plasma terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
TMF	Trial Master File
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analogue scale
V_{ss}/F	Apparent volume of distribution at steady state
WMA	World Medical Association

PROTOCOL SYNOPSIS

Protocol number:	MT-6345-E01
Protocol title:	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
Sponsor:	Mitsubishi Tanabe Pharma Development America Inc. [redacted] EU Representative: Mitsubishi Tanabe Pharma Europe Ltd [redacted]
Principal Investigator:	[redacted]
Development phase:	Phase I
Investigational Medicinal Product (IMP):	MT-6345 [redacted] and [redacted] capsules. Placebo capsule to match all active MT-6345 capsule strengths.
Reference product:	Not applicable.
Treatment duration:	Subjects in Part 1 (single ascending dose [SAD]), Part 4 (gender effect) and Part 5 (race effect) will participate in one single dose treatment period. 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 on MT-6345 (Part 2). 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 3 (multiple ascending dose [MAD]) will participate in one treatment period and receive a once daily dose of MT-6345 for at least 14 days. The duration of dosing in Part 3 may be altered based on review of emerging data from Part 1, but will not exceed 28 days.
Objectives:	**Primary Objective** To evaluate the safety and tolerability of single and multiple ascending oral doses of MT-6345 administered to healthy subjects. **Secondary Objectives** • To investigate the pharmacokinetic (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 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. [redacted]
Study design:	This is a Phase I, randomised, double-blind, placebo-controlled, single-centre study, comprising five parts. It is planned to randomise 100 subjects in this study. One additional cohort of 8 subjects and one cohort of 12 subjects may be added to Parts 1 and 3, respectively. Therefore, up to 120 subjects may be included in the study. **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 area under the plasma concentration-time curve [AUC] at the no observed adverse effect level [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 dose escalation factor applied after each cohort will not exceed five-fold for Cohorts 1 to 2, four-fold for Cohorts 2 to 3 and will not exceed three-fold thereafter. 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. **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) on the PK of MT-6345. There will be a minimum of 15 days between the last dose administration in Part 1 and 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 eight 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. **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). The same dose will be used for each cohort in Parts 2, 4 and 5.
Planned number of subjects:	Up to 100 subjects are planned to be enrolled, 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. One 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 Japanese male subjects.
Subject population:	Parts 1, 2 and 3: healthy male Caucasian subjects aged 18 to 55 years. Part 4: healthy female Caucasian subjects aged 18 to 55 years. Part 5: healthy male Japanese subjects aged 18 to 55 years.
Main inclusion criteria:	1. Able to provide written informed consent to participate in this study after reading the participant information sheet and Informed Consent Form, and after having the opportunity to discuss the study with the Investigator or designee. 2. Healthy and free from clinically significant illness or disease as determined by medical history, physical examination, laboratory and other tests at Screening and Day -1. [redacted] 5. A body weight of ≥60 kg for males and ≥50 kg for females and a body mass index (Quetelet index) ranging from 18 to 30.0 kg/m^2 inclusive at Screening and Day -1. [redacted] 8. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the Protocol restrictions and requirements. [redacted]
Main exclusion criteria:	1. Subjects with clinically significant (in the opinion of the Investigator) endocrine, thyroid, hepatic, respiratory,

	gastrointestinal, neurological, renal, cardiovascular disease, or history (within the last 5 years) of any significant psychiatric/psychotic illness disorder (including anxiety, depression and reactive depression). 2. Female subjects who are pregnant (positive pregnancy test at Screening or Day -1) or lactating. [redacted] 11. Having previously received MT-6345 as part of this study. [redacted]

	[redacted] 15. Clinically relevant abnormal medical history, physical findings or laboratory values at Screening or Day -1 that could interfere with the objectives of the study or the safety of the subject, as judged by the Investigator. [redacted] 21. Subjects who test positive for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, human immunodeficiency virus (HIV)-1 or HIV-2 antibodies at Screening. [redacted]
Endpoints:	**Primary Endpoints** • 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 QTcF). • Clinical laboratory assessments (haematology, biochemistry, coagulation and urinalysis). • Physical examination. • Part 3 only, in addition: specialist eye examination findings **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 (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_{0-24h}). • Area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-last}). • Area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$). • Terminal elimination rate constant (Kel). • Mean residence time (MRT). • Apparent oral clearance (CL/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 ($AUC_{0-\tau}$). • $AUC_{0-last.}$ • $AUC_{0-\infty}$. • Kel. • MRT. • CL/F. • Apparent volume of distribution at steady state (V_{ss}/F). • Linearity factor (LF). • Accumulation ratio (RA). • 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.

	
Statistical methods:	**Sample size:** 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. **Safety evaluation** AEs will be considered as treatment-emergent if they occur on or after the first dose administration of IMP or if a pre-dose event increases in severity following dosing. The frequency and incidence of treatment-emergent AEs (TEAEs) will be summarised by System Organ Class and Preferred Term for each dose level and by fed state, gender and race category where appropriate. Summaries will also be presented by relationship to treatment and severity of event. Serious TEAEs and TEAEs leading to discontinuation will be listed. Safety laboratory test results, vital signs, and ECG parameters will be summarised by planned sampling point and for each dose level and by fed state, gender and race category where appropriate. Other safety measurements will be summarised and/or listed according to the data type. **Pharmacokinetic data** All data will be listed. **(i) Plasma and urine concentration of MT-6345** Plasma MT-6345 concentrations will be summarised by dose level, planned time point and by fed state, gender and race where appropriate using descriptive statistics. By-subject plasma concentration versus time will be plotted as well as the mean concentration, for each dose level, and by fed state, gender and race where appropriate, using linear and semi-logarithmic scales. The concentration of MT-6345 in urine will be listed for Part 3. **(ii) Urine pharmacokinetic parameters of MT-6345** Urinary excretion and percent urinary excretion during each collection interval will be listed. Ae, Ae% and CL_R will be summarised by dose level where appropriate, using descriptive statistics. **(iii) Plasma pharmacokinetic parameters of MT-6345** The PK parameters will be derived by non-compartmental analysis using WinNonlin® software (version 6.2 or later). The PK parameters will be summarised for each dose level and by fed state, gender and race category where appropriate and time of dosing using descriptive statistics. **(iv) Dose proportionality (Part 1)** The PK parameters ($AUC_{0-\infty}$, $AUC_{0\text{-last}}$ and C_{max}) from the SAD part will be used in the exploration of dose proportionality. The overall dose proportionality will first be evaluated using the power model. A linear model will be used to fit the power model, after log-transformation of the parameter of interest (e.g., AUC [$AUC_{0-\infty}$, $AUC_{0\text{-last}}$] or C_{max}). The model will include the log–transformed dose as fixed effect.

	A point estimate and its 95% confidence interval (CI) will be derived for the slope β to evaluate dose proportionality. The goodness of fit of the linear model will also be investigated. To evaluate dose proportionality graphically, plots of AUC and C_{max} versus dose, AUC and C_{max} (expressed on the log scale) versus dose (expressed on the log scale), and dose normalised AUC and C_{max} versus dose will be produced for each individual subject and means. Details will be specified in a Statistical Analysis Plan. **(v) Food effect (Part 2)** A linear mixed model will be used to analyse log-transformed $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, with fed state (fed, fasted) as fixed effects and subject as a random effect. Difference in least square (LS) means and corresponding 90% CI will be back-transformed to obtain the estimate and CI of geometric mean ratio of fed to fasted. The reference treatment will be the corresponding dose from Part 1. **(vi) Dose proportionality (Part 3)** Dose proportionality will be assessed by AUC_{0-24} and C_{max} on Day 1 and $AUC_{0-\tau}$ and C_{max} on the last day of dosing using the power model. A linear model will be used to fit the power model after log-transformation of the parameter of interest. The model will include the log-transformed dose as fixed effect. A point estimate and its 95% CI will be derived for the slope β. **(vii) Assessment of steady state (Part 3)** The ratio of trough concentration on each day (Day 2 to Day 13) compared to trough concentration on last dosing day (anticipated as Day 14 but could be as late as Day 28) will be summarised using descriptive statistics. Mean trough concentrations versus day will also be presented with all dose levels overlaid on the same plot. **(viii) Assessment of linearity and accumulation (Part 3)** The linearity factor ($LF=AUC_{0-\tau}$[last day of dosing]/$AUC_{0-\infty}$[Day 1]) and the ratio of accumulation ($RA=AUC_{0-\tau}$[last day of dosing]/$AUC_{0-\tau}$[Day 1]) will be summarised using descriptive statistics. The LF will not be calculated if $AUC_{0-\infty}$ on Day 1 cannot be calculated precisely. **(ix) Gender effect (Part 4)** A linear model will be used to analyse log-transformed $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, with gender (male, female) as fixed effects. Difference in LS means and corresponding 90% CI will be back-transformed to obtain the estimate and CI of geometric mean ratio comparing female to male. The reference treatment will be the corresponding dose from Part 1. **(x) Race effect (Part 5)** A linear model will be used to analyse log-transformed $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, with race (Caucasian, Japanese) as fixed effects. Difference in LS means and corresponding 90% CI will be back-transformed to obtain the estimate and CI of geometric mean ratio comparing Japanese to Caucasian. The reference treatment will be the corresponding dose from Part 1.

1.5 Clinical studies

No clinical studies have been conducted to date; MT-6345-E01 is a first-in-man study.

2 STUDY OBJECTIVES 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.

[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:

- 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 ($AUC_{0\text{-}last}$).
- $AUC_{0\text{-}\infty}$.

- Terminal elimination rate constant (Kel).
- Mean residence time (MRT).
- Apparent oral clearance (CL/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 ($AUC_{0-\tau}$).
- AUC_{0-last}.
- $AUC_{0-\infty}$.
- Kel.
- MRT.
- CL/F.
- Apparent volume of distribution at steady state (V_{ss}/F).
- Linearity factor (LF).
- Accumulation ratio (RA).
- 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).

<u>QT interval assessments</u>

- 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.

[redacted]

3 STUDY DESIGN

3.1 Overall study design

This is a Phase I, randomised, double-blind, placebo-controlled, single-centre study, comprising five parts. It is planned to randomise 100 subjects in this study. One additional cohort of 8 subjects and one cohort of 12 subjects may be added to Parts 1 and 3, respectively. Therefore, up to 120 subjects may be included in the study.

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

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 ($AUC_{0\text{-}24h}$).

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 [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 [redacted] until 72 hours post-dose after the final dose. Subjects will return for outpatient visits (if the subjects are not confined to [redacted] and PK blood samples will be taken at 5 and 8 days after last dosing. Subjects will return to [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 [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 [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 [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 [redacted] until 120 hours post-dose, i.e., the morning of Day 6.

Subjects will return to [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

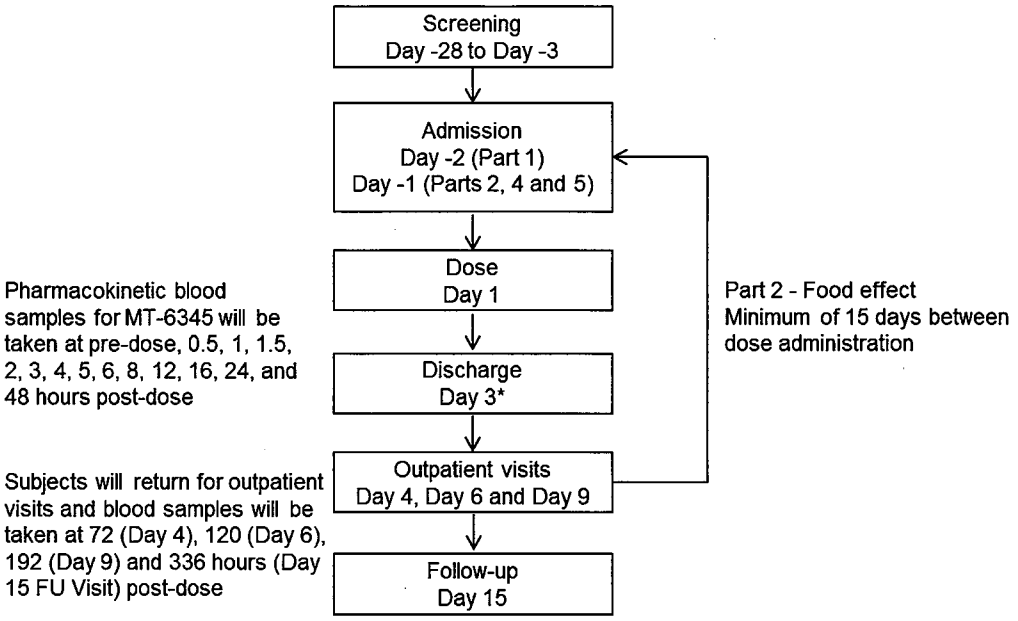
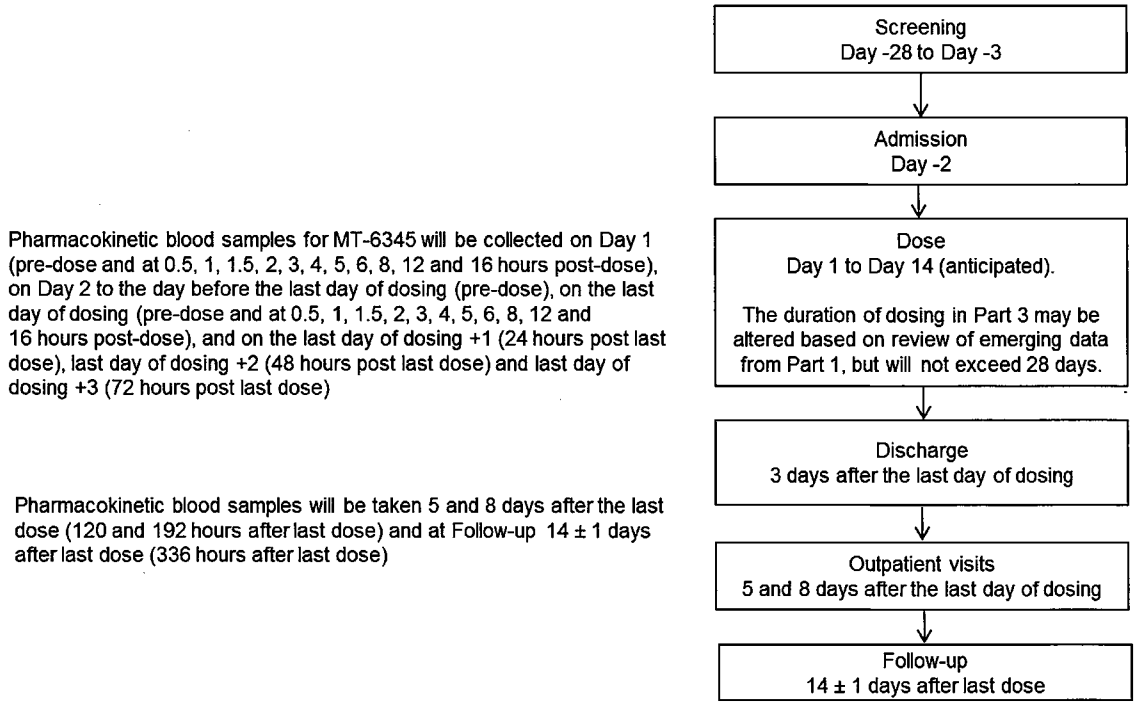


Figure 2 Study design scheme for Part 3



3.2 Rationale for study design and treatment regimens

This is a first-in-man study. The primary objectives are to obtain safety and tolerability data for MT-6345 when administered as single and multiple doses in healthy subjects. This information, together with PK data, will help to establish the dose and regimen suitable for administration in future patient studies.

A fed versus fasted comparison has been included in the study design (Part 2) to investigate the impact of food on the PK of MT-6345 in humans.

A gender comparison has been included to investigate any differences in PK between healthy male subjects and female subjects.

A race comparison has also been added to investigate the differences in PK between Caucasian and Japanese subjects (Part 5).

In line with the European Medicines Agency (EMA) Guideline on Strategies to Identify and Mitigate Risks for First in Human Clinical Trials and Early Clinical Trials with Investigational Medicinal Products (IMPs) (EMEA/CHMP/SWP 28367/07 Rev. 1 [July 2017]), all cohorts in Part 1 will have 2 sentinel subjects; one will receive MT-6345 and one will receive placebo. The remaining 6 subjects in the cohort (five receiving MT-6345 and one receiving placebo) will be dosed at least 24 hours after the sentinel subjects.

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 rationale for potentially not including sentinel dosing in Part 3 is because 1) the expected exposure after multiple dosing (both C_{max} and AUC) should be covered during the preceding SAD part of the study; unless there is the possibility of non-linear PK or accumulation at steady state that may represent a safety concern, 2) the exposure limits (C_{max} and AUC) for both SAD and MAD are listed in this Protocol and will be used to guide the dose escalation for both SAD and MAD parts of the study, and 3) a maximum duration of dosing in the MAD part is defined for every cohort.

If sentinel dosing is used in Part 3, 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).

3.2.1 Risk:benefit statement

Since MT-6345 is an investigational drug, and its safety profile in humans has not yet been investigated, all subjects receiving MT-6345 will be closely monitored until sufficient experience in humans is obtained to determine the clinical safety of MT-6345.

In a non-clinical toxicology study, changes in the eyes of both male and female rats (focal degeneration and atrophy of corneal epithelium) were observed (see Section 1.4). Therefore, all subjects will be excluded if they have a history of significant eye diseases including any history of corneal disease/disorder such as keratoconus, Fuchs' dystrophy, keratitis, dry eye or corneal ulcers/corneal grafts and/or any family history of corneal disorders such as keratoconus.

Subjects in Parts 1, 2, 4 and 5 will have an eye examination at the Screening and Follow-up Visits performed by the clinical unit's physicians.

Subjects in Part 3 will have an eye examination following the Screening Visit, which will take place at any time between day -28 and day-3. This eye examination will be conducted by a Consultant Ophthalmologist with a Certificate of Specialist training in Ophthalmology and will involve at a minimum

a full assessment of the cornea and lacrimal duct. In addition, all subjects in Part 3 will have an eye examination at approximately the halfway point during dosing (e.g. Day 7 ((+/- 2 days)) if dosing lasts for 14 days) and a final eye examination at any time between day of last dose and the Follow Up Visit, by a similarly-qualified Ophthalmologist.

During cannulation, more than one attempt may be needed to insert the cannula in a vein of a subject and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.

Electrocardiogram stickers on the subjects' chests and limbs may cause some local irritation and may be uncomfortable to remove but subjects will be closely monitored to ensure any local irritation does not persist.

3.3 Rationale for dose selection

[redacted]

Dose escalation up to [redacted] in Part 1 will only proceed following careful clinical monitoring showing acceptable safety and tolerability. In addition, dose escalation will not continue if the mean exposure limit of 45,250 ng.h/mL ($AUC_{0\text{-}24h}$) in a single subject is expected to be exceeded.

Dose escalation is planned in Part 1. The dose escalation factor applied after each cohort will not exceed five-fold for Cohorts 1 to 2, four-fold for Cohorts 2 to 3 and will not exceed three-fold thereafter. The starting dose for Cohort 1 will be [redacted] The anticipated dosing schedule is [redacted] and [redacted] A report will be prepared for each cohort in Part 1 containing safety and tolerability data (up to at least 48 hours post-dose) and PK data (up to at least 24 hours post-dose) from a minimum of 6 subjects (MT-6345 n≥4) in the preceding cohort. The Principal Investigator and Sponsor will review the data and agree whether to progress to the next dose level and dose selection.

If it is not appropriate to escalate the dose for the next planned cohort, an intermediate dose may be selected; alternatively no further dose escalation will take place (see Sections 3.4 and 4.6).

In Part 2, the effect of food on MT-6345 will be investigated. The anticipated dose level is [redacted] however, the dose will not be confirmed until safety, tolerability and PK data from the intended dose level in Part 1 has been reviewed and deemed acceptable.

In Part 3, the anticipated starting dose will be [redacted] Progression to the next dose level and dose selection will be based on available safety, tolerability and PK data from Part 1 and the preceding 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]
In Parts 4 and 5 the dose level is anticipated to be [redacted] however 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.

3.4 Dose review meetings

Dose review meetings will be held according to the Dose Review Plan to assess safety and tolerability data (up to 48 hours post-final dose for single dose parts and up to 72 hours post-final dose for MAD cohorts) and available PK data (up to 24 hours post-final dose) from a minimum of 6 subjects in Part 1 or 10 subjects in Part 3, in order to decide the dosing strategy for the subsequent cohort. Data from Part 1 will be reviewed to determine the dose for other parts. A subject is considered evaluable if they have sufficient PK and/or safety data to meet primary objectives of the study.

The safety and tolerability data reviewed at these meetings will include: vital signs, 12-lead ECG, routine clinical laboratory assessments and AEs. At meetings to review Part 3 data, the available ophthalmological findings will also be reviewed. Pharmacokinetic parameters to be reviewed will include AUC up to and including the 24-hour post-final dose sample time point.

Participants at the meetings may include the Sponsor's Responsible Physician, the Sponsor's Safety Physician, [redacted] Pharmacokineticist, the Principal Investigator and the Project Manager from both the Sponsor and [redacted] (or delegates). The meetings must be quorate and the minutes of each meeting will be filed in the Trial Master File (TMF).

Interim safety information will be provided by the Investigator to the Sponsor between each dose level in the form of a safety report. Safety reports will be quality controlled but not audited.

Interim PK reports for dose escalation between dose levels will include raw interim PK datasets and PK parameters and will be provided by [redacted] to the Sponsor. The data will be based on nominal sample times and will be presented against alias Subject Numbers so that the Sponsor and Investigator remain blinded to randomisation. Further information will be specified in a separate analysis plan for dose escalation.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

The Sponsor does not operate a Protocol waiver system for eligibility criteria.

4.1 Number of subjects

Up to 100 subjects are planned to be enrolled in the study, which may be increased to a maximum of 120 subjects if additional cohorts are included in Parts 1 and 3 of the study. The number of subjects in each part of the study is shown in Table 1.

Table 1 Number of subjects

Part		No. subjects	Cohorts	Description of subjects
1	SAD	48 (56)	Six cohorts of 8 subjects: MT-6345, n=6: placebo, n=2 (One additional cohort of 8 subjects may be enrolled)	Healthy Caucasian male 18-55 years
2	Food	8	One cohort selected from Part 1: MT-6345, n=6: placebo, n=2	Healthy Caucasian male 18-55 years
3	MAD	36 (48)	Three cohorts of 12 subjects: MT-6345, n=9: placebo, n=3 (One additional cohort of 12 subjects may be enrolled)	Healthy Caucasian male 18-55 years
4	Gender	8	One cohort: MT-6345, n=6: placebo, n=2	Healthy Caucasian females 18-55 years
5	Race	8	One cohort: MT-6345, n=6: placebo, n=2	Healthy Japanese male 18-55 years
	Total	**100 (120)**		

Abbreviations: MAD=multiple ascending dose; SAD=single ascending dose.

4.2 Recruitment methods

Subjects will be recruited from a database of volunteers at [redacted] or *via* media advertisements, if appropriate. Subjects will be recruited according to the [redacted]' Standard Operating Procedures (SOPs). All recruitment material will be approved by the Independent Ethics Committee (IEC) prior to implementation.

4.3 Inclusion criteria

A subject will be eligible for enrolment in the study if ALL of the following criteria apply:

1. Able to provide written informed consent to participate in this study after reading the participant information sheet and Informed Consent Form (ICF), and after having the opportunity to discuss the study with the Investigator or designee.
2. Healthy and free from clinically significant illness or disease as determined by medical history, physical examination, laboratory and other tests at Screening and Day -1.

[redacted]

[redacted]

5. A body weight of ≥60 kg for males and ≥50 kg for females and a body mass index (BMI) (Quetelet index) ranging from 18 to 30.0 kg/m^2 inclusive at Screening and Day -1.
6. [redacted]
7. [redacted]
8. In the Investigator's opinion, subject is able to understand the nature of the study and any risks involved in participation, and willing to cooperate and comply with the Protocol restrictions and requirements.

[redacted]

4.4 Exclusion criteria

A subject will NOT be eligible for this study if ANY of the following criteria apply:

1. Subjects with clinically significant (in the opinion of the Investigator) endocrine, thyroid, hepatic, respiratory, gastrointestinal, neurological, renal, cardiovascular disease, or history (within the last 5 years) of any significant psychiatric/psychotic illness disorder (including anxiety, depression and reactive depression).
2. Female subjects who are pregnant (positive pregnancy test at Screening or Day -1) or lactating.

[redacted]

11. Having previously received MT-6345 as part of this study.

[redacted]

15. Clinically relevant abnormal medical history, physical findings or laboratory values at Screening or Day -1 that could interfere with the objectives of the study or the safety of the subject, as judged by the Investigator.

[redacted]

21. Subjects who test positive for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, human immunodeficiency virus (HIV)-1 or HIV-2 antibodies at Screening.

[redacted]

[redacted]

4.5 Withdrawal of individual subjects

Subjects will be withdrawn from the study for the following reasons:

- The subject wishes to withdraw from further participation.
- The subject is significantly noncompliant with the Protocol.
- Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, e.g.,
  - The subject experiences intolerable AEs or serious adverse events (SAEs)
  - The subject has clinically significant changes in safety parameters at any of the post-dose time points, as confirmed with a repeat assessment performed as soon as possible after the initial out-of-range result.
  - The subject has an increase in QTcF to ≥500 ms or increase of ≥60 ms from baseline (pre-dose on Day 1), as confirmed with three consecutive ECGs taken at least 5 minutes apart in a 30-minute period.
  - Development of any clinically significant liver dysfunction, as follows:
    - ALT or AST >8 × ULN.
    - ALT or AST >5 × ULN for more than 2 weeks.
    - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN, or international normalised ratio >1.5.
    - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).
  - Part 3 only: the subject has clinically significant changes to the corneal epithelium on the eye examinations conducted by a Consultant Ophthalmologist. Clinical significance will be judged by the Investigator.
- Pregnancy in a female subject.

In addition, a subject may be withdrawn at any time for reason(s) other than those listed here. If IMP is discontinued in a subject, then the subject may still undergo all other study procedures but will not receive the IMP.

If a subject is withdrawn from the study prematurely, the date the IMP is discontinued and the reason for withdrawal will be recorded on the electronic case report form (eCRF).

In case of withdrawal of a subject from the study, the Follow-up Visit assessments should be performed, as far as possible (Section 5.2.4).

Reporting as an SAE must be considered in cases where the AE has led to a withdrawal from the study or the withdrawal is for a safety reason and, therefore, may be medically important, in accordance with Section 8.2.

Any unresolved AE or SAE will be followed up according to Section 8.9.

In the event that a subject elects not to return to the [redacted] for the Follow-up Visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject withdraws from the study at any time, the reason for withdrawal must be fully documented in the source documents and the eCRF. [redacted] personnel will document the

AEs and any other assessments in the source documents and eCRF and will make every effort to complete all required Follow-up Visit assessments.

Subjects who are withdrawn from the study following randomisation may not re-enter the study.

Subjects withdrawn from the study for non-treatment-related reasons may be replaced at the discretion of the Sponsor and Investigator. Replacement subjects will receive the treatments intended for the withdrawn subject.

4.6 Dose escalation stopping criteria

After each cohort, the Sponsor's EU Representative and the Principal Investigator will, according to the Dose Review Plan, review and assess all available PK, safety and tolerability data from all the cohorts to date in order to make a decision on the dose for the next cohort.

Doses may be changed based on emerging data. If it is not appropriate to escalate the dose for the next cohort according to the anticipated dosing schedule then the same dose (provided this dose was not considered intolerable or unsafe), a lower dose or an intermediate dose may be given.

If any of the following scenarios occur within a cohort of subjects receiving MT-6345 with a reasonable possibility of a causal relationship with MT-6345, no further dose escalation will take place:

1. Liver function tests (assessment of AST, ALT and bilirubin):
   - 2 subjects with an AST or ALT value ≥3 × ULN.
   - 2 subjects with a total bilirubin ≥2.5 × ULN (Note: the 2 subjects with elevated bilirubin do not have to be the same 2 subjects that have elevated AST or ALT).
2. Renal function tests (assessment of serum creatinine):
   - 2 subjects with serum creatinine ≥2 × ULN.
3. ECG criteria (assessed by analysis of QTcF):
   - 2 subjects demonstrate a QTcF value >500 ms and/or an increase of ≥60 ms above the baseline value (Day 1 pre-dose ECG), based on each subject having at least three consecutive ECGs taken at least 5 minutes apart in a 30-minute period.
4. Systemic exposure is predicted to have an $AUC_{0\text{-}24h}$ value ≥45,250 ng.h/mL in an individual subject.
5. Clinically significant changes to the corneal epithelium in an individual subject.

4.7 Study stopping criteria

The study will be stopped if either of the following occur:

1. A 'serious' adverse reaction (i.e., an SAE considered at least possibly related to the IMP administration) in 1 subject.
2. 'Severe' non-serious adverse reactions (i.e., severe non-serious AEs considered as, at least, possibly related to the IMP administration) in 2 subjects administered with MT-6345 in the same cohort, independent of whether or not the event is within the same System Organ Class (SOC).

Whether the event was related to the IMP administration will be determined by the Investigator. If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and IEC in the form of a substantial amendment. The study may be

resumed or terminated; however, it will not be resumed until a further substantial amendment to resume the study is submitted and approved by the MHRA and IEC.

Details on the process for confirming the above criteria, and any necessary actions, will be contained within a study-specific Safety Monitoring Plan.

4.8 Lifestyle restrictions

Subjects will be advised that they must adhere to the following restrictions:

4.8.1 Attendance

- Availability to attend visits according to the Protocol.
- Availability for overnight stays in [redacted] unit for 4 nights (Part 1), 3 nights (Parts 2, 4 and 5), 18 to 32 nights (Part 3) or 6 nights (Japanese cohort, Part 5).

4.8.2 Alcohol restrictions

- Subjects should refrain from consuming food or drink containing alcohol in the 24 hours before each visit and while confined to [redacted]
- Subjects should avoid excessive consumption (>2 units per day) of food or drink containing alcohol at all other times from the Screening Visit until the Follow-up assessment.

4.8.3 Xanthines

- Subjects should refrain from consuming food or drink containing caffeine and methylxanthine (e.g., coffee, tea, cola, energy drinks or chocolates) in the 24 hours before Day -1 until completion of the post-treatment assessments on Day 3 (Parts 1, 2, 4 and 5) or 3 days after the last day of dosing (Part 3), and in the 24 hours before each Follow-up assessment.
- Subjects should avoid excessive consumption (more than five cups of coffee or equivalent per day) of food or drink containing caffeine and methylxanthine (e.g., coffee, tea, cola, energy drinks or chocolates) at all other times from the Screening Visit until the Follow-up assessment.

4.8.4 Smoking

No smoking or use of tobacco- or nicotine-containing products (snuff, cigarettes, cigars, pipes, e-cigarettes, nicotine replacement products or chewing tobacco) is allowed in the 3 months before the first dose of IMP, during the study and until the final Follow-up assessment.

4.8.5 Contraception

Female subjects of child-bearing potential* must be willing and able to practice birth control for the duration of the study, from the Screening until 3 months after the last dose of IMP. Male subjects must be willing and able to practice birth control for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

- **Female subjects** must be willing to use a highly effective method of birth control (i.e., contraceptive measure with a failure rate of <1% per year), in conjunction with male barrier contraception (i.e., male condom with spermicide). Hormonal contraception will not be an acceptable form of contraception for Part 4 of the study due to the possibility of enzyme induction by MT-6345. Highly effective methods of contraception for female subjects participating in Part 4 of the study include:
  - Placement of an intrauterine device or intrauterine system.
  - Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. For female subjects on the study, the vasectomised male partner should be the sole partner for that subject).
  - Bilateral tubal occlusion.

- True abstinence: when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Female subjects must not donate ova from the Screening Visit until 3 months after the last administration of IMP.

- **Male subjects** with partners of child-bearing potential must use a barrier method of contraception (i.e., male condom with spermicide) in addition to a second method of acceptable contraception used by their female partners. In addition to the list of highly effective contraception methods above, other acceptable methods of contraception include:
  - Established use of oral, injected, transdermal, transvaginal or implanted hormonal methods of contraception associated with inhibition of ovulation.
  - Progesterone only oral contraception, where inhibition of ovulation is not the primary mode of action.
  - Cap, diaphragm or sponge with spermicide.

  Male subjects must not donate sperm for the duration of the study, from the time of the first dose of IMP until 3 months after the last dose of IMP.

*Note: Women are considered to be of child-bearing potential unless they meet one of the following criteria as documented by the Investigator:

- Post-menopausal for at least 1 year, confirmed by follicle stimulating hormone (FSH) assessment (>40 mIU/mL).
- Hysterectomy, bilateral oophorectomy or salpingectomy.
- Congenital sterility.

Subjects must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study. Subjects engaging in exclusively same sex sexual relations do not need to use contraception.

4.8.6 Fluid and food intake

All meals including breakfast, lunch and dinner are required to be controlled by clinical staff members on all days. While confined to the Phase I unit, subjects will receive standardised meals at scheduled times. A restricted menu will be provided to subjects. The start and stop time of the meal must be recorded in the source and where less than 100% of the meal has been consumed, the percentage consumed must be recorded in the source.

For all cohorts, lunch will be provided at approximately 4 hours post-dose, an evening meal at approximately 10 hours post-dose and an evening snack at approximately 14 hours post-dose. On subsequent non-dosing days, meals will be provided at appropriate times.

If, for technical reasons, dosing is delayed for more than 2 hours beyond the expected dosing time, subjects will receive 200 mL of Lucozade Sport at the originally scheduled dosing time, or earlier if possible.

Single dose parts: Subjects will be allowed water up to 1 hour before the scheduled dosing time and water will be allowed *ad libitum* from 1 hour post-dose. Decaffeinated fluids will be allowed *ad libitum* from lunch time on the day of dosing. Subjects will be permitted additional water to help swallow the capsules if necessary.

Multiple ascending dose part: Subjects will be allowed water up to 1 hour before each scheduled dosing time and will be allowed water *ad libitum* from 1 hour after each dose. Decaffeinated fluids will be allowed *ad libitum* from lunch time on the day of dosing until approximately 22:00 each evening (the

exact time of decaffeinated fluid restriction will depend on the time of the dosing earlier in the day as subjects must fast for 10 hours prior to the next dose). Subjects will be permitted additional water to help swallow the capsules if necessary.

During the inpatient phase, each evening subjects will be provided with a light snack and will fast from all food and drink (except water) from approximately 22:00 each night until the following morning (in Part 3 the exact time that fasting starts will depend on the time of dosing earlier in the day as subjects must fast for 10 hours prior to the next dose). On dosing days, subjects will either be dosed with MT-6345 in the fasted state (Parts 1, 3, 4 and 5) or be provided with an FDA-approved high-fat breakfast (Part 2 only) to be consumed prior to dosing. On non-dosing days, all subjects will be provided with a standard breakfast.

The FDA-approved high-fat breakfast in Part 2 should be consumed over a maximum period of 30 minutes, with dosing occurring 30 minutes after the start of breakfast. Subjects should be encouraged to eat their entire meal evenly over the 30-minute period. It is acknowledged that some subjects will take less time to eat, but dosing should still occur 30 minutes after the start of breakfast. The start and stop time of breakfast must be recorded in the source and where less than 100% of the meal has been consumed, the percentage consumed must be recorded in the source.

Multiple ascending dose part: a light breakfast will be provided at 2 hours post-dose (apart from Day 1 and the last day of dosing, when subjects will be fasted for 4 hours post-dose); on Day -1, meals will be provided according to the predicted dosing time on Day 1. Lunch will be provided at approximately 4 hours post-morning dose, dinner at approximately 10 hours post-morning dose and an evening snack at approximately 14 hours post morning dose. Meals will be provided at appropriate times on all other days.

4.8.7 Diet

A similar calorie/fat content menu will be provided to subjects for breakfasts, lunches and dinners.

- Subjects in Parts, 1, 4 and 5 will be required to fast (except for water) for at least 10 hours prior to IMP administration and will remain fasting for 4 hours post-dose.
- Subjects in Part 2 will receive an FDA-approved high-fat breakfast prior to IMP administration. The high-fat meal will consist of 800 to 1000 total calories with a ratio of nutrients of 150 calories protein, 250 calories carbohydrates, and 500 to 600 calories fat. An example of a high-fat meal would include one hash brown, two rashers of streaky bacon (grilled), one small egg (45 g) fried in 10 g of butter, two slices of white medium sliced bread with 20 g of butter and 240 mL of full fat milk. Subjects should eat this entire meal in 30 minutes or less; however, the MT-6345 tablets should be administered 30 minutes after start of the meal.
- Subjects in Part 3 will be required to fast (except for water) for at least 10 hours prior to IMP administration on all dosing days.
- No food or drink containing red wine, Seville oranges, cranberry, liquorice or grapefruit (including marmalade and fruit juices) will be allowed from 7 days before first dose of IMP until the Follow-up assessment.
- Subjects should refrain from ingesting food or drink containing poppy seeds in the 72 hours before the Screening Visit and from 7 days before the time of the first dose of IMP until the Follow-up assessment to avoid the occurrence of false positive opioid drug screen results.

4.8.8 Contact Lens Wear (Part 3 only)

- Subjects must not wear contact lenses from the baseline ophthalmological exam until discharge from the clinic.

4.8.9 Physical activity restrictions

- Subjects must not participate in heavy physical training or excessive exercise (e.g., long distance running, weight lifting or any physical activity to which they are not accustomed) from 7 days before the first dose of IMP, during the study and until the final Follow-up assessment.

4.8.10 Blood donation

- Subjects must not have donated one or more units of blood (450 mL) in the 3 months prior to Screening, or plasma in the 7 days prior to Screening, or platelets in the 6 weeks prior to Screening.
- Subjects must agree not to donate blood for 3 months after the last Follow-up assessment.

5 STUDY PLAN

Study assessments are summarised in the time and events schedule for Parts 1, 2, 4 and 5 in Table 2 and for Part 3 in Table 3 and Table 4.

Time points for assessments may be changed based on emerging data.

Table 2 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	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	
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 6.
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 4). A serum pregnancy test will be performed at Screening and a urine pregnancy test at all other time points.
5. Females 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 3 Time and events schedule for Part 3

Study Day	SCR	Treatment day		FU
	-28 to -3	Day -2 to maximum 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 4 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[4,7]	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 4). 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).

6. [redacted]

Table 4 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[2]	LDD[3]	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

Study Day	ADM	Treatment day																														
	-1	1													2	3	4	5	6	7	MDD[1]	8	9	10	11	12	13 to LDD -1[2]	LDD[3]	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													
[redacted]																																
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]																																
Urine sampling for PK[13]		<----------													---------->													<-->			
[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 Day 1; 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 +1 and 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 Day 1 (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).
12. [redacted]
13. PK urine samples for MT-6345 will be collected at Day -1 (-24 hours 0 hours), Day 1 (0 hours to 24 hours) and LDD (0 hours to 24 hours).
14. [redacted]

5.1 Subject informed consent

Prior to performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is given full and adequate oral and written information about the study and the subject must sign the ICF, as described in Section 11.2.1.

5.2 Description of study phases

Time points for assessments may be changed based on emerging data.

5.2.1 Screening

5.2.1.1 Screening (Parts 1, 2, 3, 4 and 5)

Screening assessments will be performed from Day -28 to Day -3 for Part 1 and Part 3; and from Day -28 to Day -2 for Parts 2, 4 and 5. This study permits the re-screening of a subject who has withdrawn from the study as a pre-treatment failure (i.e., subject has not been randomised/has not been treated); the reason for failure must be temporary and expected to resolve.

At Screening, subjects will be requested to attend [redacted] after a 10-hour fasting period (apart from water). Written informed consent will be obtained before any Screening procedures are performed.

The following assessments will be performed (refer to Table 2 and Table 3 for further details):

- Written informed consent.
- Demography and medical history.
- Verify inclusion/exclusion criteria.
- Physical examination (including height, weight, BMI and eye examination, and for subjects in Part 1, 2, 4 and 5, an eye examination conducted by the clinical unit's physicians).
- Subjects in Part 3 will have an eye examination conducted by a Consultant Ophthalmologist, at any time between Day -28 and Day -3. Further details of eye examinations can be found in Section 6.5.1.
- Screening for drugs of abuse, carbon monoxide breath and alcohol tests.
- Serology.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- Serum pregnancy test for females only.
- FSH test for females only.
- AE and concomitant medication recording.

5.2.2 Confinement period

5.2.2.1 Confinement period (Parts 1, 2, 4 and 5)

Subjects who successfully complete Screening will return to [redacted] unit on the evening of Day -2 for Part 1 in order to begin Holter Monitoring on Day -1. Subjects in Parts 2, 4 and 5 will return on the morning of Day -1. Inclusion and exclusion criteria will be reviewed to confirm eligibility on admission. No IMP will be administered on Day -2 or Day -1.

On Day 1, subjects who meet the study eligibility criteria will be randomised to receive IMP (MT-6345 or a matching placebo). In Part 2, study assessments e.g., ECG can be completed prior to the subject eating the FDA-approved high-fat breakfast.

[redacted] While every effort will be made to collect these data, should it be likely to affect the timely conduct of other study procedures, then one or more may be omitted without being considered a Protocol deviation.

The following assessments will be performed (refer to Table 2 for further details and time points):

Day -1

- Verify inclusion/exclusion criteria.
- Body weight and BMI.
- Screening for drugs of abuse, carbon monoxide breath and alcohol tests.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- Continuous ECG recorded for 48 hours; from approximately 24 hours pre-dose (Day -1) until 24 hours post-dose (Day 2) (Part 1 only).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- Urine pregnancy test for females only.
- [redacted]
- AE and concomitant medication recording.

Day 1 (pre-dose)

- Verify inclusion/exclusion criteria.
- Randomisation.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- Continuous ECG recorded for 48 hours; from approximately 24 hours pre-dose (Day -1) until 24 hours post-dose (Day 2) (Part 1 only).
- 12-lead ECG.
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Day 1 (post-dose)

- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature) at 1, 2, 4, 8 and 12 hours post-dose.
- Continuous ECG recorded for 48 hours; from approximately 24 hours pre-dose (Day -1) until 24 hours post-dose (Day 2) (Part 1 only).
- 12-lead ECG at 1, 2, 3 and 8 hours post-dose.
- PK blood sampling for MT-6345 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose.
- [redacted]
- AE and concomitant medication recording.

Day 2 (24 hours post-dose)

- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- Continuous ECG recorded for 48 hours; from approximately 24 hours pre-dose (Day -1) until 24 hours post-dose (Day 2) (Part 1 only).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).

- PK blood sampling for MT-6345.
- AE and concomitant medication recording.

Day 3 (48 hours post-dose)

- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

5.2.2.2 Confinement period (Part 3)

Subjects who successfully complete Screening will return to [redacted] unit on the evening of Day -2. Assessments will be performed on Day -1. Inclusion and exclusion criteria will be reviewed to confirm eligibility on admission. No IMP will be administered on Day -2 or Day -1.

On Day 1, subjects who meet the study eligibility criteria will be randomised to receive IMP (MT-6345 or a matching placebo) once daily for a minimum of 14 days.

[redacted] While every effort will be made to collect these data, should it be likely to affect the timely conduct of other study procedures, then one or more may be omitted without being considered a Protocol deviation.

Subjects will be allowed to take supervised walks on study days as agreed by the Sponsor and [redacted]

The following assessments will be performed (refer to Table 4 for further details and time points):

Day -1

- Verify inclusion/exclusion criteria.
- Body weight and BMI.
- Screening for drugs of abuse, carbon monoxide breath and alcohol tests.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG at -0.5, 1, 2, 3 and 8 hours relative to expected dose time on Day 1.
- Continuous ECG recorded from approximately 24 hours pre-dose (Day -1) until pre-dose on Day 1.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- [redacted]
- PK urine sampling for MT-6345 (-24 hours to 0 hours pre-dose).
- [redacted]
- AE and concomitant medication recording.

Day 1 (pre-dose)

- Verify inclusion/exclusion criteria.
- Randomisation.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).

- 12-lead ECG.
- Continuous ECG recorded from approximately 24 hours pre-dose (Day -1) until pre-dose on Day 1.
- PK blood sampling for MT-6345.
- [redacted]
- PK urine sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Day 1 (post-dose)

- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature) at 1, 2, 4, 8 and 12 hours post-dose.
- 12-lead ECG at 1, 2, 3 and 8 hours post-dose.
- PK blood sampling for MT-6345 at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose.
- [redacted]
- PK urine sampling for MT-6345 at 0 hours to 24 hours post-dose.
- [redacted]
- AE and concomitant medication recording.

Day 2

- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (pre-dose).
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Day 3

- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (pre-dose).
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- PK blood sampling for MT-6345.
- AE and concomitant medication recording.

Days 4, 6, 7, 9, 10, 11 and 12

- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (pre-dose).
- [redacted]
- PK blood sampling for MT-6345.
- AE and concomitant medication recording.

Day 5

- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (pre-dose).
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- PK blood sampling for MT-6345.
- AE and concomitant medication recording.

Day 8

- Body weight and BMI.
- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (at pre-dose, 1, 2, 3 and 8 hours post-dose).
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis). If dosing is extended beyond 14 days, a blood sample will be taken on Day 14 and every 7 days thereafter
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Midpoint dosing day (e.g. if duration of dosing is 14 days then should be on Day 7 (+/- 2 days))

- Eye examination conducted by a Consultant Ophthalmologist. Further details can be found on Section 6.5.1.

Day before last day of dosing (Day 13 or extended up to maximum Day 27)

- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (pre-dose).
- PK blood sampling for MT-6345.
- AE and concomitant medication recording.

Last day of dosing (Day 14 or extended up to maximum Day 28)

- Body weight and BMI.
- Vital signs (pre-dose; including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG (at pre-dose, 1, 2, 3 and 8 hours post-dose).
- Continuous ECG recorded from pre-dose to 24 hours post last dose (last day of dosing +1).
- [redacted]
- PK blood sampling for MT-6345 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose.
- [redacted]
- PK urine sampling for MT-6345 at 0 hours to 24 hours post-dose.
- [redacted]
- AE and concomitant medication recording.

Last day of dosing +1

- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).

- Continuous ECG recorded from pre-dose for the last dose to 24 hours post last dose.
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Last day of dosing +2

- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Last day of dosing +3

- Body weight and BMI.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

5.2.3 Outpatient visits

5.2.3.1 Outpatient visits (Parts 1, 2, 4 and 5)

Subjects will return for outpatient visits and PK blood samples will be taken at Day 4 (72 hours post-dose), Day 6 (120 hours post-dose) and Day 9 (192 hours post-dose). Japanese subjects in Part 5 will be discharged the morning of Day 6 and return for an outpatient visit on Day 9.

5.2.3.2 Outpatient visits (Part 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).

5.2.4 Follow-up

5.2.4.1 Follow-up (Parts 1, 2, 4 and 5)

Subjects will return to the clinic on Day 15 ± 1 day for a Follow-up Visit. The cohort of subjects selected for Part 2 will not attend the Follow-up Visit following their first treatment period (Part 1) but will attend a Follow-up Visit at Day 15 ± 1 day following their second treatment period. The following assessments will be performed (refer to Table 2 for further details):

- Physical examination (including weight, BMI and eye examination).
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- Urine pregnancy test for females only.
- PK blood sampling for MT-6345.
- AE and concomitant medication recording.

5.2.4.2 Follow-up (Part 3)

Subjects will return to the clinic 14 ± 1 days after last dose (336 hours after last dose) for a Follow-up Visit. The following assessments will be performed (refer to Table 3 for further details):

- Physical examination (including weight and BMI).
- All subjects will have an eye examination conducted by a Consultant Ophthalmologist at any time between day of last dose and the Follow-up Visit. Further details can be found in Section 6.5.1.
- Vital signs (including supine blood pressure, pulse rate, respiratory rate and oral body temperature).
- 12-lead ECG.
- Routine laboratory evaluations (haematology; biochemistry; coagulation; urinalysis).
- PK blood sampling for MT-6345.
- [redacted]
- AE and concomitant medication recording.

Subjects who are withdrawn from the study should, where possible, complete the procedures scheduled for the Follow-up Visit as soon as possible after withdrawal.

5.2.5 Post-study access to treatment

Not applicable as this is a healthy volunteer study.

5.2.6 Unscheduled visits

An unscheduled visit is defined as any visit to [redacted] outside of the Protocol-specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, measuring device failure, confirmation of out-of-range results), where the subject is seen by study personnel.

Additional unscheduled samples for safety assessments may be performed at the discretion of the Investigator, if deemed necessary. All unscheduled visits and assessments performed during the visits will be recorded in the eCRF.

6 STUDY PROCEDURES

Procedures will be performed according to the time and events schedule (Table 2, Table 3 and Table 4). A priority order will be in effect when more than one assessment is required at a particular time point and this will be described in a separate document. Time windows for relevant assessments will be described in a separate document.

6.1 Demography

Date of birth, gender, weight, height and race will be recorded.

6.2 Medical history

Any significant and relevant past conditions and any current medical conditions prior to Screening will be recorded.

6.3 Concomitant medication

At Screening, subjects will be asked what medications they have taken during the last 3 months. Medication taken within 2 weeks of Screening will be recorded in the subject's source documents as prior 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. All concomitant medications taken during the study from Screening to the final Follow-up assessment will be recorded.

6.3.1 Permitted medication

Medicines which, in the opinion of the Sponsor and Investigator, will not interfere with the study procedures or compromise safety may be used, e.g., paracetamol (acetaminophen) for mild analgesia. However, any other concomitant medication will be given only if deemed necessary by the Investigator or the subject's personal physician.

6.3.2 Prohibited medication

Subjects must not participate in any other clinical study involving administration of an IMP for the duration of the current study.

Subjects must not take any prescribed or non-prescribed systemic or topical medication (including herbal remedies) unless, in the opinion of the Investigator and Sponsor's physician, the medication will not interfere with the study procedures or compromise safety. Occasional use of paracetamol (acetaminophen) for mild analgesia is permitted.

6.3.3 Rescue medication

There is no known antidote to MT-6345. Full resuscitation facilities will be available at all times. There is no other requirement for the availability of additional medication other than that routinely available at ward level and within the pharmacy of the clinical unit.

6.4 Pharmacokinetic assessments

In single-dose parts, blood samples for MT-6345 will be collected 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) and 192 hours (Day 9) post-dose and at the Day 15 Follow-up Visit (336 hours).

In Part 3, blood samples for MT-6345 will be collected on Day 1 (pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose), Day 2 to the day before the last day of dosing (pre-dose), the last day of dosing (pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 16 hours post-dose), and on the last day of dosing +1 (24 hours post last dose), last day of dosing +2 (48 hours post last

dose) and last day of dosing +3 (72 hours post last dose). 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 Follow-up 14 ± 1 days after last dose (336 hours after last dose).

The timings of all PK and [redacted] may be subject to change based on the ongoing review of data. Additional blood samples may be taken from each subject; however, the maximum volume of blood withdrawn per subject will not exceed the limit detailed in Section 6.7. Any changes to the scheduled times of PK or [redacted] will be agreed between the Sponsor and Investigator and documented in the TMF.

Not all cohorts will have samples taken for [redacted] Samples for [redacted] will be taken from at least two cohorts in Part 3 and these cohorts will be selected based on emerging PK data from Part 1.

Sample handling details will be described fully in a separate document.

Contingency samples will be retained at [redacted] Phase I unit and shipped at the request of the Sponsor. If not required, the contingency samples will be destroyed only upon the written request of the Sponsor.

Blood and urine samples will be packed in dry ice and sent by courier from [redacted]. (PK samples) and [redacted], MTPC [redacted]).

The analysis will be performed only on samples from subjects receiving active drug. Results from the [redacted] will be reported separately.

6.4.1 Collection of blood samples for pharmacokinetic analysis of MT-6345 and [redacted]

Blood samples will be collected via direct venepuncture in a suitable forearm vein or via cannulation in the wrist or suitable forearm vein. The actual date and time of each blood sample will be recorded in the eCRF.

For each PK and [redacted], one blood sample of approximately 2 mL will be collected to ensure there is sufficient plasma for primary and contingency samples.

Pharmacokinetic and [redacted] will be sent by courier from [redacted] to [redacted] and [redacted], MTPC. Contingency samples will be shipped separately to the primary samples.

6.4.2 Collection of urine samples for pharmacokinetic analysis of MT-6345 and [redacted]

Subjects will be required to empty their bladders approximately 30 minutes prior to dosing and immediately after blood sampling at the end of each collection period. The actual date, time and volume of each urine collection period will be recorded in the source documents and eCRF.

For each PK assessment, two urine samples will be taken from the volume of urine collected (one as a primary sample and one as a contingency sample).

Pharmacokinetic and [redacted] will be sent by courier from [redacted] to [redacted] and [redacted] MTPC. Contingency samples will be shipped separately to the primary samples.

6.5 Safety assessments

Please refer to Section 8 for details of AE management.

The timings of all measurements to be performed during the study may be subject to change based on the ongoing review of safety, tolerability and PK data. All changes will be agreed between the

Sponsor and Investigator and documented in the TMF. The IEC will be notified of the changes, if appropriate.

6.5.1 Physical examination

A full physical examination, including body weight and height, will be assessed at Screening and Follow-up Visits.

The full physical examination will consist of a routine assessment of major body systems: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory and 'other'.

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 AE.

In addition, subjects in Parts 1, 2, 4 and 5 will have an eye examination at the Screening and Follow-up Visits performed by the clinical unit's physicians to include a check of the eyelid/external appearance of the eye, visual acuity, visual fields, light reflex, accommodation and examination of the retina and optic disc with an ophthalmoscope.

Subjects in Part 3 will have an eye examination following the Screening Visit, which will take place at any time between day -28 and day-3. This eye examination will be conducted by a Consultant Ophthalmologist with a Certificate of Specialist training in Ophthalmology; and will involve at a minimum a full assessment of the cornea and lacrimal duct. In addition, all subjects in Part 3 will have an eye examination at approximately the halfway point during dosing (e.g. Day 7 (+/- 2 days) if dosing lasts for 14 days) and a final eye examination at any time between day of last dose and the Follow Up Visit, by a similarly-qualified Ophthalmologist.

Furthermore, if any subject in any study part experiences eye symptoms following dosing with IMP, they will be referred to a specialist in ophthalmology if the symptoms are deemed clinically significant by the Investigator. If a subject experiences eye signs or symptoms outside of normal working hours, which are of an urgent nature (e.g., vision changes), they will be referred to A&E for immediate review, with follow up by a specialist in ophthalmology, if required.

Contact lens use and/or use of glasses by subjects will be recorded in the medical history and physical examination sections of the eCRF.

Subjects in Part 3 must not wear contact lenses from the baseline ophthalmological exam until discharge from the clinic.

6.5.2 Vital signs

Vital signs will be assessed according to Table 2, Table 3 and Table 4 but may be changed based on emerging data. Subjects will undergo an assessment of supine blood pressure, supine pulse rate, respiratory rate and oral body temperature.

Supine blood pressure will be measured in triplicate using an automatic blood pressure recording device with an appropriate cuff size after the subject has rested for at least 5 minutes in a supine position. Measurements will be made at least 1 minute apart and the same arm will be used for all measurements where possible. The Investigator will perform an overall evaluation for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)' or 'abnormal not clinically significant' (NCS). Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed, if needed.

6.5.3 Electrocardiogram

A 12-lead ECG will be performed according to Table 2, Table 3 and Table 4 but may be changed based on emerging data after the subject has rested for at least 5 minutes in the supine position.

The Investigator will perform an overall evaluation of the ECG for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

Continuous 12-lead ECG data will be obtained from subjects in Parts 1 and 3 only, at the time points indicated in Table 2 and Table 4. If analysis of the continuous 12-lead ECG data is subsequently performed, it is anticipated that triplicate 10-second 12-lead ECGs will be extracted at time points prior to PK collection times after at least 5 minutes rest in order to facilitate concentration-QTc effect modelling. Data may be analysed following completion of the study to investigate the potential effect of MT-6345 on QTc. This will be fully described in a separate document.

6.5.4 Routine laboratory evaluations

Blood and urine samples will be collected for routine clinical laboratory safety evaluations according to Table 2, Table 3 and Table 4 but may be changed based on emerging data. The laboratory safety evaluations performed during the study are presented in Table 5.

Additional laboratory safety evaluations will be performed at other times, if judged to be clinically appropriate, or if the ongoing review of the data suggests a more detailed assessment of laboratory safety evaluations is required. Any changes to the scheduled times of laboratory safety tests will be agreed with the Sponsor and documented in the TMF.

The Investigator will perform a clinical assessment of all laboratory safety data.

Table 5 Routine laboratory evaluations

Haematology:	
Haemoglobin	Mean corpuscular haemoglobin
Haematocrit	Mean corpuscular haemoglobin concentration
Platelet count	Mean corpuscular volume
Red blood cell count	White blood cell count and differential
Biochemistry:	
Alkaline phosphatase	Cholesterol
Aspartate aminotransferase	Triglycerides
Alanine aminotransferase	High density lipoprotein-cholesterol
Gamma-glutamyl transpeptidase	Low density lipoprotein-cholesterol
Potassium	Protein (total)
Sodium	Albumin
Chloride	Creatine kinase
Inorganic phosphate	Creatinine
Glucose	Follicle stimulating hormone[1]
Urea	Human chorionic gonadotrophin[2]
Bilirubin (direct and total)	
Coagulation:	
Prothrombin time	Activated partial thromboplastin time
International normalised ratio	
Urinalysis:	
Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood	
Human chorionic gonadotrophin[2]	
Microscopic examination[3]	
Serology:	
Hepatitis B surface antigen	Human immunodeficiency virus -1 and -2 antibodies
Hepatitis B core antibody	Hepatitis C virus antibody
Drugs of abuse screen:	
Methadone, cocaine, barbiturates, tetrahydrocannabinol, benzodiazepines, amphetamines, opiates, carbon monoxide and alcohol breath tests	

[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.

Blood samples will be analysed by The Doctors Laboratory using commercially available kits. If microscopy is required, a urine sample will be sent to The Doctors Laboratory. Urine tests will be performed by Investigator site personnel using commercially available kits. Laboratory safety assessments will be performed according to The Doctors Laboratory SOPs. A complete list of laboratories and procedures for the handling of samples will be described in full in the Laboratory Manual.

6.6 [redacted]

For Part 3, blood samples for the assessment of [redacted] will be collected via cannulation or direct venepuncture in a suitable forearm vein at the time points indicated in Table 3 and will be sent by courier from [redacted] to [redacted] The actual date and time of each blood sample will be recorded in the source documents and eCRF.

6.7 Total blood volume

The approximate total blood volume taken per subject is given in Table 6 and Table 7.

Table 6 Blood volumes – Parts 1, 2, 4 and 5

Procedure	Sample volume (mL)	No. of samples	Total volume (mL)
Haematology	2	5	10
Biochemistry	5	5	25
Coagulation	4.5	5	22.5
Pharmacokinetics	2	18	36
		Overall total	**93.5***

* For subjects in Part 2, the amount of blood taken will be approximately twice this volume (blood sampling volumes for Treatment Periods 1 and 2 combined).

Table 7 Blood volumes - Part 3

Procedure	Sample volume (mL)	No. of samples*	Total volume (mL)*
Haematology	2	9 (11)	18 (22)
Biochemistry	5	9 (11)	45 (55)
Coagulation	4.5	9 (11)	40.5 (49.5)
Pharmacokinetics (MT-6345)	2	42	84
[redacted]	2	15	30
[redacted]	4	4	16
		Overall total	**233.5 (256.5)**

Abbreviations: [redacted]
* The number of samples and total volume of blood for MT-6345 PK assessment are based on 14 days of dosing. Values in parentheses are applicable if dosing is extended to a maximum of 28 days.

The number and timing of samples may be amended following any interim PK parameter estimations. However, in this case, the total blood volume for each subject will not exceed 550 mL in a 4-week period. The first 0.5 mL of blood withdrawn via cannula will be discarded.

[redacted]

[redacted]

7 STUDY TREATMENT

7.1 Investigational Medicinal Product

A description of the IMP is given in Table 8.

Table 8 Investigational Medicinal Products

	MT-6345	Placebo
Dosage form	Capsule	Capsule
Description	Swedish Orange Hard Capsule	Swedish Orange Hard Capsule
Unit dose strength	[redacted] and [redacted]	Placebo to match MT-6345 [redacted] and [redacted]
Dosage[1]	**Part 1:** [redacted] and [redacted] **Parts 2, 4 and 5:** [redacted] **Part 3:** [redacted] and [redacted]	Not applicable
Route of administration	Oral	Oral
Treatment duration	**Parts 1, 2, 4 and 5:** single dose **Part 3:** multiple doses (Days 1 to 14 up to a maximum of 28)	**Parts 1, 2, 4 and 5:** single dose **Part 3:** multiple doses (Days 1 to 14 up to a maximum of Day 28)
Dosing instructions	Capsule(s) to be swallowed with at least 240 mL water	Capsule(s) to be swallowed with at least 240 mL water
Storage conditions	Store below 25°C	Store below 25°C

[1] Anticipated doses shown; may be modified based on emerging data.

MT-6345 capsules and placebo to match capsules will be manufactured by MTPC, Japan.

IMP will be imported, Qualified Person (QP) certified and shipped to [redacted] by [redacted], UK (trading as PCI). The Sponsor will provide the necessary documentation to show that the capsules have been manufactured and tested according to Good Manufacturing Practice together with a Batch Certificate, Certificates of Analysis and a transmissible spongiform encephalopathy Statement.

Individual subject doses will be packed in opaque high-density polyethylene bottles with desiccant-attached polypropylene caps, labelled and QP certified by [redacted]

All labelling will comply with applicable regulatory requirements.

7.1.1 Compliance

The IMP will be administered orally by designated qualified study personnel at [redacted] who will check the subject's mouth and/or hands to confirm that the dose was swallowed. The Investigator, or suitably qualified staff member, will supervise the administration of IMP and the exact time of dosing will be recorded in the subject's source documents and eCRF.

7.1.2 Shipping, receipt, handling and storage

IMP will be shipped from [redacted] to [redacted] according to the required storage conditions.

On receiving a shipment of IMP at [redacted], the Investigator or designee will conduct an inventory check and complete a supplies receipt document, the original of which will be retained at [redacted]; a copy must be returned to the Sponsor or designee as soon as possible. The Investigator or designee will maintain a record of all IMP received and returned.

At [redacted] the IMP will be stored below 25°C in a locked, restricted-access area. Refrigerated storage is not required. A temperature log recording the daily maximum/minimum temperature of the storage area will be maintained. Any IMP storage temperature deviations will be reported to the Sponsor as soon as possible.

7.1.3 Dispensing

The unblinded QP or designee at the clinical site will receive a copy of the final randomisation schedule for preparation of the IMP and preparation of the treatment allocation list.

On each dosing occasion, the Investigator or designee will provide the subject with the allocated dose. A record of the IMP dispensed to each subject will be maintained by the Investigator or designee in an Accountability Log.

7.1.4 Accountability, returns and destruction

During the study, the Investigator or designee will record the quantities of IMP dispensed and returned in an Accountability Log. IMP accountability (reconciliation) will be checked by the Sponsor. IMP is to be used only for this Protocol and not for any other purpose.

All unused IMP must be stored at [redacted] until permission has been given by the Sponsor for it to be returned to [redacted]

Following completion and review of all IMP accountability records and resolution of any discrepancies on-site, the Investigator will return all IMP to [redacted] for destruction according to their local procedures. Confirmation of destruction will be provided to the Sponsor.

7.2 Subject identification

Each subject will be assigned a unique Screening Identification Number by [redacted] Upon randomisation, each subject will also be assigned a unique Randomisation Number. Both the Screening Number and the Randomisation Number will be documented in the subject's source documents and eCRF.

Subjects who are withdrawn for non-treatment related reasons may be replaced at the discretion of the Sponsor and Investigator. The substitute subject will receive the same treatment assigned to the subject they replace. Subjects withdrawn as a result of treatment-emergent AEs (TEAEs) thought to be causally related to the IMP will generally not be replaced.

A list identifying the subjects by the Screening Number and Randomisation Number will be kept in the Investigator Site File.

7.3 Procedures for assigning subjects to treatment groups

Randomisation will be performed according to a computer-generated randomisation list, and subjects will be given a corresponding Randomisation Number.

Randomisation will take place after confirmation of inclusion and exclusion criteria prior to the first administration of IMP on Day 1.

The randomisation code will be produced by the Statistics Department at [redacted] Prior to the start of the study, a copy of the master randomisation code will be supplied to the pharmacy staff at [redacted] and the unblinded MTPE Clinical Supplies Department.

7.4 Maintenance of the study blind and unblinding

This is a double-blind study. Treatment assignment will not be known to the subjects, the Sponsor or the staff who are involved in the clinical evaluation of the subjects and the analysis of data. The randomisation schedule and disclosure envelopes will be generated by an unblinded statistician at

[redacted] according to [redacted] SOPs. The unblinded statistician will not be involved in any decisions relating to populations for analysis prior to unblinding.

For each subject, sealed treatment decode envelopes will be held in a secure area by the Investigator and Sponsor. The sealed code should not normally be broken for reasons other than safety or in an emergency. Should the Investigator wish to break the code for such reasons, he/she should ideally consult the Sponsor in advance. If this is not possible, the Investigator may break the code and document the date and reason for breaking the blind without prior discussion with the Sponsor. The Sponsor should be notified as soon as possible thereafter. If the blind is broken for any individual subject, the subject must be withdrawn from the study, and any procedures accompanying withdrawal should be performed (Section 4.5).

If the study stopping criteria appear to be met, the Sponsor will unblind individual subject allocations to confirm stopping criteria have been met. The specific mechanism for unblinding will be outlined in a separate document.

The Sponsor will authorise release of the unblinded randomisation list at the end of the study.

Prior to database lock and unblinding, all original randomisation materials, including the original final signed and dated randomisation schedule, will be held by the Quality Assurance (QA) department at [redacted]. The Data Sciences department will not have access to the randomisation schedule before database lock and unblinding.

A copy of the final randomisation schedule will also be made available to MTPE Clinical Supplies and the laboratory performing the bioanalysis to allow selective analysis of drug concentrations. The blind of the study will be broken after the study database has been locked and the safety population has been defined for that part. Any request for issue of the randomisation schedules must be made using a randomisation disclosure form.

MT-6345 and matching placebo capsules are identical in appearance. MT-6345 and matching placebo will be packaged identically and suitably labelled to maintain the blind.

8 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time written informed consent is obtained until the end of the Follow-up Period will be recorded in the source documents and eCRF. Even if the AE is assessed by the Investigator as not related to IMP, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as 'baseline' if they occur before the administration of IMP. AEs 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.

At each study visit, after the subject has had an opportunity to spontaneously mention any problems, the Investigator should inquire about the occurrence of AEs. The questioning should be open-ended and non-leading.

8.1 Definition of an adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

8.2 Definition of a serious adverse event

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event.

Medical and scientific judgement should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse. These should also usually be considered serious.

The term 'life-threatening' refers to an event/reaction in which the subject was at risk of death at the time of the event/reaction; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

Admission to a hospital as a new inpatient is deemed as meeting this criterion, even when the length of hospital stay was less than 24 hours. Transfer to other departments of the same hospital due to a newly emerged event during the hospitalisation (e.g., transfer from the psychiatry ward to the internal medicine ward, from the internal medicine ward to the coronary intensive care unit, or from the neurology ward to the tuberculosis ward) is also counted as hospitalisation.

SAEs will be recorded and reported as described in Section 8.7.

8.3 Severity of adverse events

The severity of AEs will be classified according to the following criteria:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes discomfort and interferes with the subject's general condition.
Severe:	The event causes considerable interference with the subject's general condition and may be incapacitating.

To ensure no confusion or misunderstanding of the difference between the terms 'serious' and 'severe', which are not synonymous, the following note of clarification is provided:

The term 'severe' is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as 'serious', which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.4 Relationship of adverse events to Investigational Medicinal Product

The causal relationship of the AE to IMP will be determined as either 'reasonable possibility' or 'no reasonable possibility' defined as:

Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship possible, and other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

No Reasonable Possibility – The relationship of the clinical event to the IMP makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

8.5 Clinical laboratory abnormalities and other abnormal assessments

Laboratory abnormalities which are clinically significant will be recorded as AEs or SAEs. The Investigator will exercise medical judgement in deciding whether abnormal laboratory values are clinically significant.

If an abnormal laboratory value or assessment is clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values.

All clinically significant abnormal laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or until they are judged by the Investigator to be no longer clinically significant.

8.6 Recording and reporting of adverse events

All AEs, regardless of the relationship to IMP, occurring from the time written informed consent is obtained from a subject until the end of the Follow-up Period or the withdrawal of the subject from the study will be recorded.

All AEs will be recorded on an AE form in the eCRF. Reports should contain a description of the event, date and time of onset, date and time of resolution, severity, treatment required, relationship to IMP, action taken with the IMP, outcome and whether the event is classified as serious.

The Investigator will evaluate the severity of the AEs (as defined in Section 8.3) and will assess the causality between the AEs and the IMP (as defined in Section 8.4).

Pre-existing illnesses, which started prior to entry and is still ongoing at the start of the study, will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded as medical history.

If the Investigator becomes aware of any new safety information, or any safety information which appears to be either study or IMP related after the final Follow-up Period, then they must notify the Sponsor immediately.

8.7 Recording and reporting of serious adverse events

All SAEs occurring from the time written informed consent is obtained from a subject until the end of the safety Follow-up Period or the withdrawal of the subject from the study must be notified to the Sponsor, by email or fax, using a paper SAE form **within 24 hours** of the Investigator becoming aware of the SAE.

The SAE report should be completed as thoroughly as possible, including an assessment of causality. All such reports will identify subjects by unique code numbers assigned to the study participants, rather than by the subjects' names, personal identification numbers, or addresses.

The reporting contact for SAEs is as follows:

[redacted]

In case of any email problems, the SAE form will be sent to the MTPE Safety Department via fax to:

Fax: [redacted]

The Sponsor will comply with the applicable regulatory requirements related to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the Regulatory Authorities and IEC.

8.8 Pregnancy

If a female subject who has been exposed to the IMP becomes pregnant, the course and outcome of the pregnancy should be monitored and documented. Where possible, if a female partner of a male subject who has been exposed to the IMP becomes pregnant and the subject provides this information, then the pregnancy will be documented based on information provided by the subject.

Pregnancy occurring in a female subject, or a female partner of a male subject, who has been exposed to the IMP, although not classified as an SAE, must be reported using the same timelines and contact details as an SAE (Section 8.7) but via a paper pregnancy form. If the outcome or course of the pregnancy involves an SAE (e.g., a congenital anomaly), then a paper SAE form needs to be completed in addition to the paper pregnancy form. Termination of pregnancy for medical reasons, spontaneous abortion and congenital birth defects should always be reported as SAEs.

8.9 Follow-up of adverse events

The Investigator should follow-up subjects with AEs/SAEs, until the event has resolved or stabilised and any abnormal laboratory values have returned to baseline; or until they are judged by the Investigator to be no longer clinically significant. In the case of death, if possible a pathologist's full report should be supplied.

8.10 Reference safety information

The reference safety information for this clinical study is the MT-6345 Investigator's Brochure[11]. All serious adverse reactions will be deemed unexpected and therefore reportable as SUSARs.

8.11 Overdose

Any subject who takes an overdose should be given the standard medical care (see Section 6.3.3).

If the subject takes a dose which is greater or more frequent than that specified in the Protocol (with or without associated symptoms), this must be reported to the Sponsor immediately or within 24 hours of awareness via a paper SAE form (using the contact details in Section 8.7).

If the subject experiences any associated symptoms as a result of the overdose, the Investigator will record this as a separate AE/SAE.

9 DATA COLLECTION AND PROCESSING

9.1 Data collection

Subject data will be collected on individual eCRFs and will be substantiated by source documents (such as laboratory reports, medical records or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF and the eCRF will be considered the source document.

Prior to the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor or designee will provide training for completion of the eCRF. The eCRF will be completed according to guidelines provided by the Sponsor or its designee in writing, electronically and/or verbally.

Completed eCRFs will be reviewed by the Study Monitor to ensure data accuracy, completeness and consistency. Any discrepancies found during the eCRF review or during data validation and/or QA reviews of the data by data management or other functions are to be clarified by the Investigator (or his/her designated personnel).

The Investigator or designee must record all required subject data using the previously specified data collection method defined by the Sponsor. An explanation must be documented for any missing data. The Investigator must electronically sign and date the eCRFs attesting to his/her responsibility for the quality of all data recorded, and that the data represents a complete and accurate record of each subject's participation in the study. The data collected in the eCRF will be returned to the Sponsor, and an electronic copy will be retained by the Investigator.

9.2 Case report form completion

The eCRF will be presented as an electronic casebook comprising a series of electronic forms. The Subject Number should always be indicated and date (and time, if applicable) of each assessment should be entered in the eCRF.

The eCRFs must be completed in a timely manner so that this does not delay the ongoing data validation, review and quality control. The final, completed eCRF for each subject must be electronically signed and dated by the Investigator on the appropriate eCRF form to signify that he/she has reviewed the electronic casebook and certifies it to be complete and accurate.

The eCRF will feature a special means for correcting errors in the previously entered data. A complete audit trail of the original entries, changes and deletions, session dates and times and the credentials of the eCRF user who performed the operation will be maintained by the system.

9.3 Data processing

The data collected on the eCRFs will be captured in a specially constructed and validated database. The data will be validated using both manual and electronic means. Clarification of data will be requested from the Investigator site as required. An audit trail of the original database entries, changes and deletions, session dates and times and the credentials of the database user who performed the operation will be maintained by the system. The completed database will be quality assured and locked to prevent further changes. A full database extract will be made available for statistical analysis according to the methods outlined in Section 10 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health Organisation Drug Dictionary. Versions of the dictionaries used will be documented in the Data Management Plan and SAP.

10 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 Determination of sample size

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.

10.2 Analysis sets

The statistical analysis will be based on separate analysis sets, defined as follows:

Randomised population:	All subjects randomised.
Safety population:	All randomised subjects who received at least one dose of IMP.
PK analysis set:	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 safety population will be used for all safety summaries. Pharmacokinetic assessments will be performed on the PK analysis set.

10.3 Statistical analysis

10.3.1 General considerations

The SAP, containing detailed data handling, analysis methods, outputs (tables, figures and listings), will be developed and approved prior to database lock. Additional analysis may be performed if deemed necessary. Any deviations from the planned analysis will be described and justified in a separate document and in the Clinical Study Report (CSR).

All subjects who received placebo for Part 1 will be pooled into a single placebo group (dose level 0) and all subjects who received placebo for Part 3 will be pooled into a single placebo group (dose level 0) for the final statistical analysis. The assignment of subjects to the various analysis sets will be listed and summarised. Summaries for Parts 2, 4 and 5 will be done by treatment group and by status, with corresponding dose cohort from Part 1.

All variables will be summarised by treatment group/cohort. Unless otherwise stated, continuous data will be summarised descriptively using N (number of subjects), n (number of observations), mean, standard deviation (SD), minimum, median and maximum. Categorical data will be summarised using frequency tables (frequency and percentage). The term "log-transformation" refers to the natural logarithmic transformation throughout the SAP.

All individual subject data will be listed.

10.3.2 Data handling

Procedures for the handling of any missing, unused or spurious data will be described in the SAP.

10.3.3 Analysis of demography and other baseline subject characteristics

The number of subjects screened, randomised and included in each analysis population will be reported.

Demographic data and baseline characteristics such as age, ethnicity/race, height, body weight, BMI, smoking and alcohol use will be summarised. No formal statistical analysis of demographic or baseline characteristics will be performed.

Age will be calculated as the integer difference in years from date of birth to informed consent date. Medical history will be coded using MedDRA latest version and medical history and concomitant medications will be listed by subject.

10.3.4 Analysis of primary endpoint

The objective of the evaluation is to investigate any effects of MT-6345 on safety and tolerability variables. All safety variables will be summarised. All safety data will be listed. There will be no formal inferential statistical analysis of the safety data.

10.3.4.1 Adverse events

A by-subject AE data listing including start/stop times, verbatim term, Preferred Term, SOC, dose level, severity, seriousness, relationship to treatment and outcome will be provided. All AEs that start before dosing but do not worsen after dosing will be classified as baseline AEs and will be listed only. All TEAEs, i.e., AEs which start on or after dosing, will be tabulated. In the tabulations, numbers of subjects with TEAEs and numbers (occurrences) of TEAEs will be counted separately. The frequency and incidence of TEAEs will be summarised by fed state, gender and race category where appropriate.

The following summaries of TEAEs will be presented:

- Summary of AEs by SOC and Preferred Term.
- Summary of AEs by SOC, Preferred Term and severity of event.
- Summary of AEs by SOC, Preferred Term and relationship to treatment.

The above TEAEs summaries will be produced for each dose level and placebo for Part 1 and for each dose level and placebo for Part 3. For Parts 2, 4 and 5, TEAEs will be presented by each dose of MT-6345 and placebo separately, alongside the corresponding dose and placebo from Part 1.

Serious TEAEs and TEAEs leading to IMP discontinuation will be listed.

10.3.4.2 Vital signs and electrocardiograms

Vital signs and 12-lead ECG variables and changes from baseline will be summarised (N, n, mean, SD, median, minimum and maximum) at each time point for each study Part by dose level and by fed state, gender and race category, where appropriate.

The baseline for the vital sign parameters and 12-lead ECG measurements will be the last valid assessment obtained on Day 1 prior to the administration of double-blind IMP.

10.3.4.3 Routine safety laboratory tests

Laboratory variables and changes in laboratory variables from baseline (Day -1) will be summarised (N, n, mean, SD, median, minimum and maximum) at each time point for each study Part by dose level and by fed state, gender and race category, where appropriate.

Urinalysis variables will be listed by subject and time point.

Values outside the normal ranges (provided with the laboratory report), will be flagged in the subject data listings.

10.3.4.4 Physical examination

Physical examination data will be listed by subject. Changes in physical examinations will be described in the text of the CSR.

10.3.5 Analysis of secondary endpoints

All data will be listed.

10.3.5.1 Plasma and urine concentration (MT-6345)

Plasma MT-6345 concentrations will be summarised by dose level, planned time point and by fed state, gender and race where appropriate using descriptive statistics.

By-subject plasma concentration versus time will be plotted as well as the mean concentration, for each dose level, and by fed state, gender and race where appropriate, using linear and semi-logarithmic scales.

The concentration of MT-6345 in urine will be listed for Part 3.

10.3.5.2 Urine pharmacokinetic parameters (MT-6345)

Urinary excretion and percent urinary excretion during each collection interval will be listed. Ae, Ae% and CL_R will be summarised by dose level where appropriate, using descriptive statistics.

10.3.5.3 Plasma pharmacokinetic parameters (MT-6345)

The PK parameters will be derived by non-compartmental analysis using WinNonlin® software (version 6.2 or later).

The PK parameters will be summarised for each dose level and by fed state, gender and race category where appropriate and time of dosing using descriptive statistics.

10.3.5.4 Dose proportionality (Part 1)

The PK parameters ($AUC_{0-\infty}$, AUC_{0-last} and C_{max}) from the SAD part will be used in the exploration of dose proportionality. The overall dose proportionality will first be evaluated using the power model. A linear model will be used to fit the power model, after log-transformation of the parameter of interest (e.g., AUC [$AUC_{0-\infty}$, AUC_{0-last}] or C_{max}). The model will include the log-transformed dose as fixed effect. A schematic representation of the proposed model is included below:

$$\text{Log (AUC or } C_{max}) = \alpha + \beta \cdot \log (\text{Dose}) + \varepsilon$$

Where α and β are the regression coefficients and ε is the error term.

A point estimate and its 95% confidence interval (CI) will be derived for the slope β to evaluate dose proportionality. The goodness of fit of the linear model will also be investigated.

To evaluate dose proportionality graphically, the following plots will be produced for each individual subject and means:

- AUC and C_{max} versus dose.
- AUC and C_{max} (expressed on the log scale) versus dose (expressed on the log scale).
- Dose normalised AUC and C_{max} versus dose.

10.3.5.5 Food effect (Part 2)

A linear mixed model will be used to analyse log-transformed $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, with fed state (fed, fasted) as fixed effects and subject as a random effect. Difference in least square (LS) means and corresponding 90% CI will be back-transformed to obtain the estimate and CI of geometric mean ratio of fed to fasted. The reference treatment will be the corresponding dose from Part 1.

10.3.5.6 Dose proportionality (Part 3)

Dose proportionality will be assessed by AUC_{0-24} and C_{max} on Day 1 and $AUC_{0-\tau}$ and C_{max} on the last day of dosing using the power model.

A linear model will be used to fit the power model after log-transformation of the parameter of interest. The model will include the log-transformed dose as fixed effect. A point estimate and its 95% CI will be derived for the slope β.

10.3.5.7 Assessment of steady state (Part 3)

The ratio of trough concentration on each day (Day 2 to Day 13) compared to trough concentration on last dosing day (anticipated as Day 14 but could be as late as Day 28) will be summarised using descriptive statistics. Mean trough concentrations versus day will also be presented with all dose levels overlaid on the same plot.

10.3.5.8 Assessment of linearity and accumulation (Part 3)

The linearity factor ($LF=AUC_{0-\tau}$[last day of dosing]/$AUC_{0-\infty}$[Day 1]) and the ratio of accumulation ($RA=AUC_{0-\tau}$[last day of dosing]/$AUC_{0-\tau}$[Day 1]) will be summarised using descriptive statistics.

The LF will not be calculated if $AUC_{0-\infty}$ on Day 1 cannot be calculated precisely.

10.3.5.9 Gender effect (Part 4)

A linear model will be used to analyse log-transformed $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, with gender (male, female) as fixed effects. Difference in LS means and corresponding 90% CI will be back-transformed to obtain the estimate and CI of geometric mean ratio comparing female to male. The reference treatment will be the corresponding dose from Part 1.

10.3.5.10 Race effect (Part 5)

A linear model will be used to analyse log-transformed $AUC_{0-\infty}$, AUC_{0-last} and C_{max}, with race (Caucasian, Japanese) as fixed effects. Difference in LS means and corresponding 90% CI will be back-transformed to obtain the estimate and CI of geometric mean ratio comparing Japanese to Caucasian. The reference treatment will be the corresponding dose from Part 1.

10.3.5.11 Continuous 12-lead Holter Electrocardiogram

Data from continuous 12-lead Holter monitoring will be analysed following completion of the study to investigate the potential effect of MT-6345 on QTc interval or stored for future analysis and will be reported separately.

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11 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

11.1 Good Clinical Practice

The Investigator will ensure that this study is conducted in compliance with the 2013 (Fortaleza, Brazil) revision of the 1964 Declaration of Helsinki. This study will also be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines. This study will also be carried out in accordance with regional and local legal requirements. Before the first subject is enrolled in the study, all ethical and legal requirements will be met.

11.2 Investigator responsibilities

11.2.1 Informed consent

Prior to undergoing any study-specific procedure, all legally competent subjects must consent in writing to participate. An ICF will be given to each subject, which will contain all regulatory-required elements, all ICH-required elements, and data protection information, when applicable, in language that is understandable to the subject.

The process of obtaining the informed consent will be in compliance with all regulatory regulations, ICH requirements and local laws.

Either the Investigator or a designated person, qualified to meet any applicable local regulations, who is equally knowledgeable about the study will explain the aims, methods, anticipated benefits and potential hazards of the study and any discomfort it may entail. The review must be in a form understandable to the subject. A corresponding written explanation will also be provided and the subject allowed sufficient time to consider the study information.

If the subject is willing to participate in the study, the ICF will be signed and dated by the subject, the Investigator and, if applicable, the designated person who explained the nature of the study. The subject will receive a copy (together with the information sheet) and the original ICF will be retained with the study records at the Investigator site.

The date (and time, if required) on which the ICF is signed by the subject must be recorded in the eCRF.

The Investigator or his/her designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the Investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IEC. The Investigator site personnel must use the amended ICF for all new subjects and repeat the consent process with the amended ICF for any ongoing subjects.

11.2.2 Ethical and regulatory approval

The study was conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP as described in:

1. Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General

Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
2. ICH Harmonised Tripartite Guidelines for Good Clinical Practice 1996.
3. Directive 2001/83/EC: The Community Code Relating to Medicinal Products for Human Use, 06 November 2001 (as last amended by Directive 2012/26/EU of 25 October 2012).
4. Directive 2001/20/EC: The Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use (as last amended by Regulation No 596/2009 of 18 June 2009).
5. Directive 2005/28/EC: Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products for Human Use, as Well as the Requirements for Authorisation of the Manufacturing or Importation of Such Products.
6. The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No 1031) and subsequent amendments.
7. Association of the British Pharmaceutical Industry Guidelines for Phase I Trials (2018).

The Investigator and Sponsor will sign this Protocol to confirm agreement to abide by it.

Before any study-related procedure is performed on a subject, all IEC and regulatory approvals of this Protocol will be obtained. While the study is ongoing and at study completion/discontinuation, the Sponsor or Investigator will submit information to the regulatory authority and IEC(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs.
- Periodic reports on the progress of the study.
- Notification of the end of study or early termination.
- Final study summary upon completion or closure.

The Sponsor will ensure that any SUSARs from this study and other studies with this IMP are reported promptly to the regulatory authorities.

It will be the responsibility of the Sponsor to report fatal or life-threatening SUSARs to the MHRA and the EMA as soon as possible, but no later than 7 calendar days after they first become aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider. It will be the responsibility of the Investigator to report fatal or life-threatening SUSARs to the IEC as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.

It will be the responsibility of the Sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became aware of the reaction. This responsibility may be delegated to the pharmacovigilance provider. It will be the responsibility of the Investigator to report other SUSARs to the IEC as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

If it is necessary to substantially amend the Protocol during the study, proper notification will be made to the regulatory authorities and IECs in the form of a Protocol Modification. Non-substantial amendments will not require notification to be made to the regulatory authorities and IECs. Protocol Modification requiring IEC/regulatory approval may be implemented only after a copy of the IEC's approval/favourable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). A Protocol Modification that is intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor, regulatory authority and/or IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Any Protocol or other deviations that occur during the study will be documented and reported to the Sponsor. Depending on the nature of the deviation, this may be reported to the appropriate regulatory authority and IEC.

11.2.3 Source document requirements and document access during the study

The Investigator must retain a comprehensive and centralised filing system of all study-related documentation (including, but not limited to: essential documents, copies of Protocols, CRFs, source data such as original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator/institution will permit study-related monitoring, audits, IEC reviews and regulatory inspections providing direct access to source data/documents.

11.2.4 Study records retention

Study-related documentation must be kept for at least 25 years or until notified by the Sponsor. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

11.3 Study monitoring

In accordance with applicable regulations, GCP, and the procedures of the Sponsor or its designees, the Study Monitor will periodically contact the Investigator site, and conduct on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrolment rate, and data quality at the Investigator site. Through these visits and frequent communications (e.g., letter, email, and telephone), the Study Monitor will verify that the investigation is conducted according to Protocol, regulatory and Sponsor requirements.

The Investigator will allow the Study Monitor direct access to all relevant documents, and allocate his/her time and the time of his/her personnel to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the Investigator site personnel prior to the start of the study to discuss the Protocol and data collection procedures.

At study closure, the Study Monitor will conduct all activities as indicated in Section 11.5.

11.4 Quality assurance and auditing

Authorised representatives of the Sponsor, IEC and/or regulatory authorities may conduct an audit or inspection of this study either during or after completion. In such cases, the Investigator will give the auditor/inspector direct access to all relevant documents and source data, and will allocate his/her time and the time of his/her personnel as may be required to discuss findings and any relevant issues.

11.5 End of study and site closure

The end of the study is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor.
- Completion of data clarifications and/or resolutions.
- Accounting, reconciliation, and final disposition of used and unused IMP.
- Review of Investigator site study records for completeness.

Any unresolved AE or SAE will be followed up according to Section 8.9.

11.6 Premature discontinuation of the study

The Sponsor reserves the right to discontinue the study because of safety concerns, ethical issues or serious and/or persistent non-compliance with the Protocol.

Dose escalation stopping criteria are described in Section 4.6.

Study stopping criteria are described in Section 4.7.

If the study is suspended or terminated, the Sponsor will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IEC, and providing the reason(s) for the suspension or termination of the study.

For all subjects, the Follow-up Visit assessments should be performed, as far as possible (Section 5.2.4).

Any unresolved AE or SAE will be followed up according to Section 8.9.

In the event that a subject elects not to return to the clinic for the end of study visit, the Investigator must make every effort to contact the subject to review all AEs. In the event that a subject withdraws from the study at any time, the reason for withdrawal must be fully documented in the source documents and the eCRF. The Investigator site personnel will document the AEs and any other assessments in the source documents and will make every effort to complete all required end of study assessments.

In addition, all general Investigator site activities required for the scheduled end of study and site closure should be completed, as described in Section 11.5.

11.7 Liability and insurance

Please refer to the written study information given to the subject.

12 DISCLOSURE OF DATA

12.1 Confidentiality

A Subject Screening and Enrolment Log will be completed at each Investigator site for all subjects who signed an ICF. A Subject Identification Log, documenting the subjects' names, will be completed and retained at each Investigator site for all subjects enrolled in the study.

Subject names will remain confidential and will not be included in the database supplied to the Sponsor or its designee. If the subject name appears on any document collected, e.g., hospital discharge summary, the name must be obliterated before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects will give explicit permission for representatives of the Sponsor, regulatory authorities, and the IEC to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with laws and regulations. All personnel involved in the study will observe and work within the confines of local data protection regulations.

All information concerning the product as well as any information such as clinical indications for the IMP, its formula, methods of manufacture and other scientific data relating to it, that have been provided by the Sponsor or designee, and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

12.2 Publication

By signing the study Protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

The Sponsor or designee will prepare a final report on the study. The Investigator's right to publish or present any information on the study, and publication procedures to be followed, will be defined in the Investigator site agreement.

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