Study Protocol

Protocol Number: MT-8554-A01

A randomized, double-blind, placebo-controlled study to assess the effect of MT-8554 on the frequency and severity of vasomotor symptoms in postmenopausal women

Protocol Version: Final incorporating Amendment 5
Protocol Amendment Date: 22 March 2018

NCT number: NCT03291067

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A randomized, double-blind, placebo-controlled study to assess the effect of MT-8554 on the frequency and severity of vasomotor symptoms in postmenopausal women

IND Number:	[redacted]
EudraCT Number:	
Investigational Medicinal Product:	MT-8554
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310
Protocol Version:	Final incorporating Amendment 5
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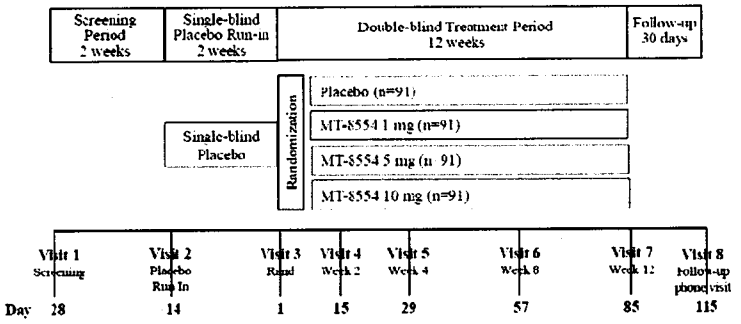
PROTOCOL SYNOPSIS

Protocol number:	MT-8554-A01
Protocol title:	A randomized, double-blind, placebo-controlled study to assess the effect of MT-8554 on the frequency and severity of vasomotor symptoms in postmenopausal women
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310
Development phase:	Phase II
Indication:	Treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause
Investigational Medicinal Product:	• [redacted] (MT-8554): [redacted] and [redacted] mg capsules • Placebo to match MT-8554 [redacted] and [redacted] mg capsules
Treatment regimen:	• Dose: MT-8554 1, 5, or 10 mg, or placebo • Route: Oral • Frequency: Once daily before bedtime
Treatment duration:	Subjects will participate in the following treatment periods: • Single-blind Placebo Run-in period: 2 weeks • Double-blind Treatment period: 12 weeks
Objectives:	**Primary Objective:** To assess the efficacy of MT-8554 on the frequency and severity of VMS in postmenopausal women. **Secondary Objectives:** • To assess the dose-response effect and the minimum effective dose of MT-8554 on the frequency and severity of VMS. • To assess the effect of MT-8554 on subjective sleep quality as measured by diary or insomnia questionnaires. • To assess the safety and tolerability of MT-8554.
Subject population:	Naturally or surgically-induced menopausal women with moderate to severe VMS defined as follows: Moderate: sensation of heat with sweating, able to continue activity Severe: sensation of heat with sweating, causing cessation of activity

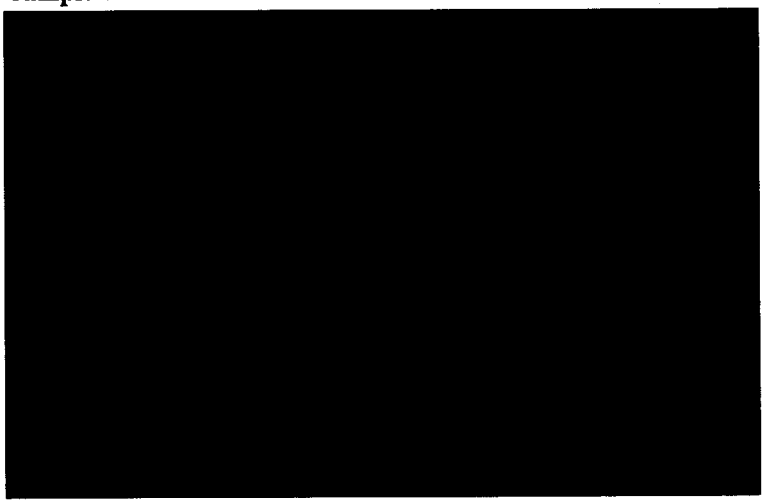
Planned number of subjects:	Approximately 364 subjects will be randomized in the study, with a target of 91 subjects in each treatment arm.
Study design:	
Study methodology:	This is a Phase II randomized, double-blind, placebo-controlled study for dose selection in women with naturally or surgically induced menopause with moderate to severe VMS. Subjects meeting eligibility criteria will be enrolled in a 2-week single-blind Placebo Run-in period. All eligible subjects will receive single-blind placebo once daily before bedtime. Following the Placebo Run-in period, subjects meeting eligibility criteria will enter the 12-week, placebo-controlled Double-blind Treatment period. The Double-blind Treatment period has 4 arms including: placebo and MT-8554 1, 5, and 10 mg. A single daily dose of study medication will be administered before bedtime. Subjects who complete through Week 12 may be enrolled into the open-label extension (OLE) study (MT-8554-A02) to receive MT-8554 for a further 52 weeks. An End of Study (EOS) Follow-up visit will be conducted by phone for safety follow-up 30 days after the end of the Double-blind Treatment period for subjects who do not enroll into the OLE study (MT-8554-A02). Total duration is 20 weeks, inclusive of the Screening and Follow-up periods. A planned interim assessment for safety, and a planned interim analysis for efficacy (futility) and safety will be conducted during the study; enrollment will proceed without interruption. [redacted] The primary endpoint will be evaluated at Weeks 4 and 12. Study medication compliance will be assessed. Non-compliance is defined as taking [redacted] of study medication during any evaluation period (visit to visit).

Main inclusion criteria:	1. Provide written informed consent to participate in this study. 2. Subjects must be post-menopausal women who meet at least 1 of the following criteria: • Spontaneous amenorrhea for ≥12 months (without an alternative cause) • Spontaneous amenorrhea for at least 6 months (without an alternative cause) and with follicle stimulating hormone (FSH) levels >40 mIU/mL (Note: FSH may be retested once within the Screening window for subjects ineligible due solely to this criterion) • Documented bilateral salpingo-oophorectomy ≥6 weeks, with or without hysterectomy • Total or supracervical (partial) hysterectomy without bilateral salpingo-oophorectomy, and with FSH levels >40 mIU/mL (Note: FSH may be retested once within the Screening window for subjects ineligible due solely to this criterion) 3. Subjects who have 7 or more moderate to severe VMS per day, or 50 or more moderate to severe VMS per week (based upon at least 2 weeks of daily VMS diaries during the Screening period.) 4. Have a consistent bedtime on at least 5 days per week starting at least the week before Screening and expect for the remainder of the study. 5. In the Investigator's opinion, subject is able to understand the nature of the study and any risk involved in participation, and is willing to cooperate and comply with the protocol restrictions and requirements including transvaginal ultrasound and endometrial biopsy. In addition to the above, for subjects who have participated in the Placebo Run-in period, the following criterion must be met before randomization: 6. Subjects whose mean VMS frequency (as measured by the subject's VMS diary) during the Placebo Run-in period does not drop by more than 50% from the mean level reported for entire duration (at least 2 weeks) of the Screening period. 7. Subjects with >50% of days with VMS diary data entry during each week of the Placebo Run-in period.
Main exclusion criteria:	1. Subjects with a history of undiagnosed abnormal vaginal bleeding, or any cancer within 5 years except for basal cell carcinoma. 2. Subjects with a history of Hepatitis B, Hepatitis C or HIV. 3. Subjects with a history of psychiatric illness, excessive alcohol intake or use of recreational drugs who are unsuitable for study

	enrollment and compliance in the opinion of investigator. 4. Subjects exhibiting or with a history of severe adverse reaction or allergy to MT-8554. 5. Subjects exhibiting or with a history of clinically significant lactose intolerance. 6. Subjects with peripheral vascular disease or disorders with associated vasculopathies (i.e. Raynaud's). 7. Subjects with clinically significant conditions which could interfere with the objectives of the study or the safety of the subject, as judged by the Investigator. 8. Subjects with endometrial thickness of ≥5 mm as measured by baseline transvaginal ultrasound performed at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization, assessed locally by the site. (Note: subjects qualifying based on transvaginal ultrasound will proceed to endometrial biopsy) 9. Subjects with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2.0 × upper limit of normal (ULN) above the reference range at Screening or start of the Placebo Run-in period (Visit 2). (Note: may be retested once within the Screening window for subjects ineligible due solely to these criteria.) 10. Subjects who have received any of the following estrogen or estrogen/progestin containing products: (No washout permitted during the study) • One week prior to Screening for vaginal hormonal products (rings, creams, gels). • Four weeks prior to Screening for transdermal estrogen alone or estrogen/progestin products. • Eight weeks prior to Screening for oral estrogen and/or progestin therapy. • Eight weeks prior to Screening for intrauterine progestin therapy. • Three months prior to Screening for progestin implants and estrogen alone injectable drug therapy. • Six months prior to Screening for estrogen pellet therapy or progestin injectable drug therapy. 11. Subjects who have received any of the following medications within 2 weeks of Screening: • Use of gabapentin, clonidine, sedatives, or hypnotics. • Herbal or dietary supplements, including black cohosh, soy, phytoestrogens, or over-the-counter agents known to possibly have an effect on VMS.

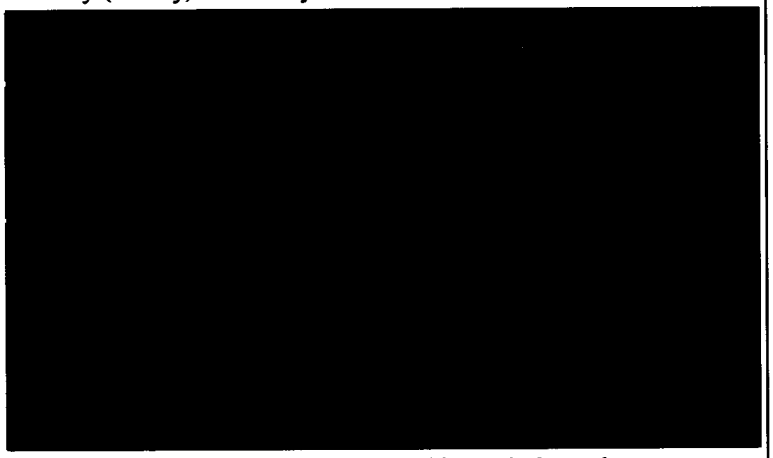
	12. Subjects who have received any of the following medications within 7 days prior to the start of the Placebo Run-in period (Visit 2): • [redacted] • Any other medication that could potentially interfere with the study procedures or compromise safety as judged by the Investigator. 13. Treatment with antidepressants which either initiated or required dose adjustments within 6 months of Screening. Subjects with antidepressants prescribed for the treatment of VMS and those using paroxetine will be excluded. 14. Subjects of childbearing potential. 15. Subjects who have participated in any study with an investigational study medication within 12 weeks (or, if relevant, 5 half-lives of that study medication, whichever is the longer) prior to the start of Placebo Run-in period (Visit 2). 16. Subjects with an abnormal (pre-defined histological categories)* result from baseline endometrial biopsy performed at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization. Subjects with insufficient tissue for diagnosis will not be qualified. (Note: Subjects with insufficient tissue for diagnosis may be retested once within the time window.) *Note: The histological categories are based on 2003 draft FDA guidance.
Study Restrictions ***Life style change and Restricted Medication***	Subjects will need to abide by various lifestyle restrictions, such as limiting alcohol, caffeine and methylxanthine intake, fasting for 6 hours after dosing at the night prior to study visits. [redacted] Subjects must not take any prescribed or non-prescribed systemic or topical medication (including herbal or dietary supplements) known to possibly have an effect on VMS or sleep during the study. Such drugs include, but not limited to estrogen, gabapentin, clonidine, progestin, black cohosh, soy, phytoestrogens, sedatives, and hypnotics. Antidepressants prescribed for the treatment of VMS and paroxetine are prohibited during the study period. Other antidepressants are permitted as long as the doses are stable for 6 months or more prior to Screening and no dose adjustments are anticipated during the study period.

Endpoints:	**Co-Primary Efficacy Endpoints** • Change from baseline in the average daily frequency of moderate to severe VMS, defined as the sum of the number of moderate to severe VMS during 1 week divided by number of days with data. The daily score here and below are average scores from a 7-day period. Details will be defined in the Statistical Analysis Plan (SAP). • Change from baseline in the average daily severity score of mild to severe VMS. Baseline VMS severity score is defined as (2xFmo + 3xFse)/(Fmo + Fse), and VMS severity score for a specific week during the double-blind treatment period is defined as (1xFmi + 2xFmo + 3xFse)/(Fmi + Fmo + Fse), where Fmi, Fmo, and Fse are the daily frequencies of mild, moderate, and severe VMS, respectively, during each applicable study week. Co-primary endpoints will be evaluated at Week 4 and Week 12. **Secondary Efficacy Endpoints** • Proportion of responders at Weeks 4 and 12 (i.e., subjects with cutoff number* or greater reduction in the average daily frequency of moderate and severe VMS compared to baseline) • Time to response, defined as time (in weeks) from randomization to the first time the subject meets responder criteria (i.e., cutoff number* or greater reduction from baseline in the average daily frequency of moderate and severe VMS) *Note: The cutoff number will be calculated using anchor-based method. The cutoff number is defined as numerical value to maximize the sensitivity and the specificity, using Patient Global Impression of Change (PGIC) as the anchor. • Change from baseline to Weeks 4 and 12 in the Insomnia Severity Index (ISI) total score **Other Efficacy Endpoints** • PGIC at Weeks 4 and 12 • Change from baseline to Weeks 4 and 12 in the Pittsburgh Sleep Quality Index (PSQI) • Change from baseline to Weeks 4 and 12 in the Menopause-Specific Quality of Life (MENQOL) • Change from baseline to Weeks 4 and 12 in the 36-Item Short Form Health Survey (SF-36) • Change from baseline in the average daily severity score of moderate to severe VMS at Weeks 4 and 12, defined as

	2xFmo + 3xFse **Pharmacokinetic (PK) assessments** Blood samples to assess plasma concentrations of MT-8554 will be performed at 5 visits during the Double-blind Treatment period. **Safety assessments** • Physical examination (including breast safety evaluation) • Vital signs (blood pressure, pulse and tympanic body temperature) • ECG parameters (including cardiac intervals: heart rate, PR, QRS, QT, QTcF and QTcB) • Clinical laboratory assessments (hematology, biochemistry, coagulation, and urinalysis) • Reproductive hormones (luteinizing hormone [LH], follicle stimulating hormone [FSH], and estradiol [E2]) • Adverse events (AEs) • Endometrial safety (endometrial thickness, as measured by transvaginal ultrasound, and incidence of endometrial hyperplasia, as measured by endometrial biopsy) • Depression and anxiety as measured by 8-Item Patient Health Questionnaire (PHQ-8) and the 7-item Generalized Anxiety Disorder questionnaire (GAD7), respectively
Statistical methods:	**Sample size considerations**  **Analysis Populations** • Randomized Population includes all subjects randomized. • Safety Population includes all randomized subjects who received at least 1 dose of study medication. • Intent-to-treat (ITT) population: includes all randomized

	subjects who have at least 1 post-baseline efficacy assessment. • Per-protocol (PP) population: includes all ITT subjects who do not have any major protocol deviations. • PK population: includes all randomized subjects who receive at least 1 dose of MT-8554 and who have at least 1 post-dose value for plasma concentration without important protocol deviations which may affect the PK of MT-8554. **Statistical Methods** The statistical analysis will be performed using SAS® version 9.2 or higher. The ITT population will be used for all clinical efficacy analyses; the PP population will also be used for the primary and secondary efficacy endpoints for confirming robustness. The Safety population will be used for all safety summaries. PK assessments will be performed using the PK population. All formal statistical tests will be done at the 5% 2-sided significance level. Point estimates will have 2-sided 95% confidence intervals (CIs) where applicable. Where appropriate, variables will be summarized descriptively (frequency and percent will be summarized for categorical variables; mean, standard deviation [SD], median, minimum, and maximum will be presented for continuous variables) by study visit and by treatment group. Primary Endpoint: *Main Analysis* Change from baseline to Week 4 and Week 12 in the average daily frequency of moderate to severe VMS will be analyzed using a repeated measures analysis of covariance (ANCOVA) model with an unstructured covariance structure. The analysis model will include baseline value of the endpoint as a covariate; weeks, treatment, antidepressant using (Y,N), and interaction between antidepressant using (Y,N) and treatment as fixed effect. Relevant covariates will also be included in the model. If the normality assumption for the model is not met, a non-parametric method such as a ranked analysis of variance (ANOVA) will be performed. The sensitivity analysis will be conducted using primary analysis model with applicable covariates for ITT subjects without using antidepressants. Similar analyses will be conducted for VMS severity. Comparison between each dose of MT-8554 and placebo will also be conducted using a repeated measures ANCOVA model. Point estimates and 95% CIs for the difference between each active dose and placebo will be obtained.

	Secondary Analysis The primary endpoints will also be analyzed using Maximum Contrast Methods with baseline value of the endpoint as a covariate, or slope approach, as an analysis of the dose-response relationship. The detail will be specified in the SAP. The primary endpoints will also be analyzed using an ANCOVA model. Secondary endpoints: After the main analyses for all co-primary endpoints successfully show the treatment effect, efficacy analyses for the secondary endpoints may be continued in a fixed order as deemed appropriate as follows: 1. Proportion of responders at Weeks 4 and 12 (i.e., subjects with cutoff number* or greater reduction in the average daily frequency of moderate and severe VMS compared to baseline) 2. Time to response, defined as time (in weeks) from randomization to the first time subjects meet responder criteria (i.e., cutoff number* or greater reduction from baseline in the average daily frequency of moderate and severe VMS) *Note: The cutoff number will be calculated using anchor-based method. The cutoff number is defined as numerical value to maximize the sensitivity and the specificity, using PGIC as the anchor 3. Change from baseline to Weeks 4 and 12 in the ISI total score The proportion of responders will be analyzed using a logistic regression model with treatment as fixed effect and baseline as covariate. The time to response will be analyzed with a log-rank test for each MT-8554 arm with placebo, with treatment as fixed effect and baseline as covariate. The VMS severity score and ISI will be analyzed using a procedure similar to the main analyses for co-primary endpoints. Other efficacy endpoints: Summary statistics will be presented for the change from baseline to Week 12 in Menopause-Specific QOL. Other efficacy endpoints will be summarized by treatment groups using descriptive statistics. Subgroup analysis: The primary analysis model with applicable covariates will be conducted for ITT subjects who used antidepressants during the study. More subgroup analyses may be defined in the SAP. Safety evaluation: AEs are considered as treatment-emergent if they occurred after administration of the first dose of randomized study medication or if a pre-dose event increases in severity following dosing. The

	frequency and incidence of treatment-emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall. Summary listings will be constructed by relationship to study medication and by maximum severity. Serious TEAEs and TEAEs leading to study medication discontinuation will be provided as listings. Vital signs, ECG parameters, and clinical laboratory results will be summarized by treatment group and planned sampling point. Other safety measurements (e.g., endometrial and breast safety evaluations) will be summarized according to the data type. Pharmacokinetics evaluation: All PK data will be listed and summarized using the number of observations, mean, SD, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. PK concentrations will be summarized by treatment and planned sampling time. In addition, the data from pharmacokinetic (PK) assessments will be summarized and used in combination with those obtained from other clinical studies in a population PK analysis to evaluate PK profiles in subjects with VMS. Interim analysis In addition to on-going safety monitoring, there will be one planned interim assessment for safety and one planned interim analysis for efficacy (futility) and safety.  The interim analysis will be conducted by an independent statistician supporting the DMC, who will evaluate the interim analysis results with unblinded data. The DMC will review the data and provide recommendations to the Sponsor.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve extrapolated to infinity
BUN	Blood urea nitrogen
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical study report
CV	Coefficient of variation
CV%	Coefficient of variation percentage
DMC	Data Monitoring Committee
E2	Estradiol
ECG	Electrocardiogram
eCRF	Electronic Data Collection Form
EOS	End of study
EOT	End of treatment
FDA	Food and Drug Administration
Fmi	Daily frequency of mild VMS
Fmo	Daily frequency of moderate VMS
Fse	Daily frequency of severe VMS
FSH	Follicle stimulating hormone
GAD7	7-Item Generalized Anxiety Disorder questionnaire

Abbreviation	Definition
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCVAb	Hepatitis C virus antibody
HDL-C	High density lipoprotein-cholesterol
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IMP	Investigational medicinal product
IND	Investigational New Drug Application
ISI	Insomnia Severity Index
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein-cholesterol
LH	Luteinizing hormone
LLOQ	Lower limit of quantification
LS mean	Least squares mean
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause-Specific Quality of Life questionnaire
MsFLASH	Menopausal Strategies: Finding Lasting Answers to Symptoms and Health
MTDA	Mitsubishi Tanabe Pharma Development America, Inc.
NCS	Not clinically significant

Abbreviation	Definition
NOAEL	No observed adverse effect level
OLE	Open label extension
PGIC	Patient Global Impression of Change
PHQ-8	8-Item Patient Health Questionnaire
PK	Pharmacokinetic(s)
PP	Per-Protocol
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred term
QOL	Quality of life
QP	Qualified Person
OSA	Obstructive sleep apnea
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cells
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse event
$t_{½}$	Apparent elimination half-life in plasma
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
t_{max}	Time at which C_{max} occurs
ULN	Upper limit of normal
US	United States
VMS	Vasomotor symptoms
WBC	White blood cells
WHO	World Health Organization
WMA	World Medical Association

TABLE OF CONTENTS

In-text Tables

In-text Figures

SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MT-8554-A01

A randomized, double-blind, placebo-controlled study to assess the effect of MT-8554 on the frequency and severity of vasomotor symptoms in postmenopausal women

The Protocol has been designed according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Code of Federal Regulations. It has undergone both medical and scientific review by competent Sponsor personnel. The study will be initiated at the site(s) only after Institutional Review Board approval of the necessary essential documents and study procedures will not be initiated until the subject has signed the approved Subject Information and Informed Consent Form(s).

Sponsor Signatory:

[redacted]

Early Development Team Leader for MT-8554,
Clinical Development

Mitsubishi Tanabe Pharma Development America, Inc.
525 Washington Boulevard, Suite 400
Jersey City, New Jersey 07310

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Sponsor Signatory:

[redacted]

Vice President and Head, Clinical Development

Mitsubishi Tanabe Pharma Development America, Inc.
525 Washington Boulevard, Suite 400
Jersey City, New Jersey 07310

SIGNATURE PAGE (STATISTICIAN)

Protocol Number: MT-8554-A01

A randomized, double-blind, placebo-controlled study to assess the effect of MT-8554 on the frequency and severity of vasomotor symptoms in postmenopausal women

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

Statistician:

[redacted]

Associate Director, Biostatistics

Mitsubishi Tanabe Pharma Development America, Inc.
525 Washington Boulevard, Suite 400
Jersey City, New Jersey 07310

SIGNATURE PAGE (PRINCIPAL INVESTIGATOR)

Protocol Number: MT-8554-A01

A randomized, double-blind, placebo-controlled study to assess the effect of MT-8554 on the frequency and severity of vasomotor symptoms in postmenopausal women

I confirm that I have read this Protocol and understand its contents. I agree to fully comply with its requirements. I understand it and will conduct the study in accordance with the procedures described in this protocol and the principles of GCP as described in 21 CFR, Parts, 50, 56, and 312, as well as any applicable local requirements.

I agree to make no changes to the conduct of the study as defined by the Protocol without the prior authorization of Mitsubishi Tanabe Pharma Development America, Inc. in the form of a Protocol Modification and without the appropriate Federal Drug Administration and Institutional Review Board approvals.

Address of Institution: _____

_____

_____

_____

Signed: _____

Print Name: _____

Title: _____

Date: _____

1 INTRODUCTION

MT-8554 [redacted] is a selective transient receptor potential melastatin 8 (TRPM8) antagonist, discovered by Mitsubishi Tanabe Pharma Corporation. Based on the compound's mechanism of action, development of MT-8554 for the treatment of vasomotor symptoms (VMS), neuropathic pain and other relevant diseases is currently under consideration.

TRPM8 is a member of transient receptor potential cation channel and is expressed in both C and Aδ fibers of primary afferent neurons. It is also expressed in the bladder and male genital tract. TRPM8 plays an essential role in the sensation of environmental cold[1].

MT-8554 is an orally active, potent and selective TRPM8 antagonist with a good safety profile in animals and has been shown to be safe and well tolerated in recently completed Phase I clinical studies[2].

It has been proposed that VMS may be triggered by small increases in core body temperature in peri- or post-menopausal women[3]. A decrease in intra-abdominal body temperature of around 1°C compared with that of time-matched controls was observed in rats and monkeys following administration of MT-8554[2]. Therefore, MT-8554 may have the potential to reduce core body temperature and decrease the frequency and severity of VMS. Since VMS are associated with sleep disturbance[4,5] it is proposed that MT-8554 may also have the potential to improve sleep quality through its effects on VMS. Hence, this study will also assess the effect of MT-8554 on VMS and sleep.

1.1 Non-clinical pharmacology

[redacted]

1.2 Non-clinical safety pharmacology

[redacted]

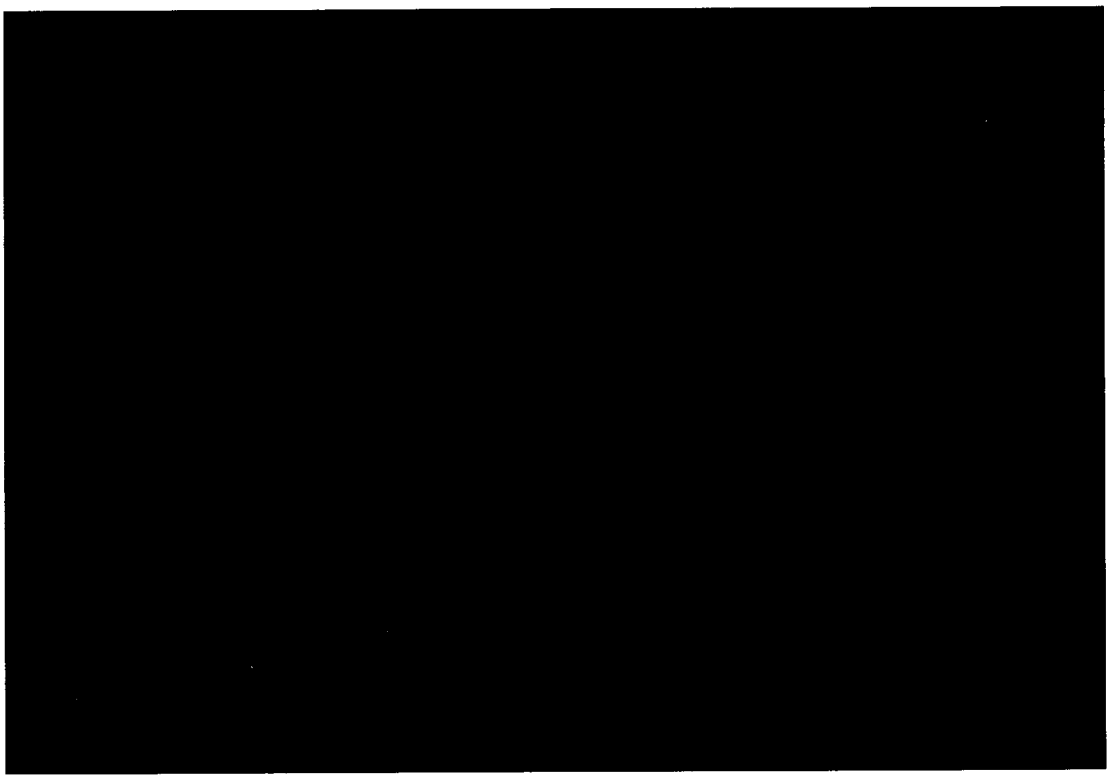
[redacted]

1.3 Non-clinical toxicology

[redacted]

1.4 Clinical studies

[redacted]



2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

2.1.1 Primary objective

To assess the efficacy of MT-8554 on the frequency and severity of VMS in postmenopausal women.

2.1.2 Secondary objectives

- To assess the dose-response effect and the minimum effective dose of MT-8554 on the frequency and severity of VMS.
- To assess the effect of MT-8554 on subjective sleep quality as measured by diary or insomnia questionnaires.
- To assess the safety and tolerability of MT-8554.

2.2 Study endpoints

2.2.1 Co-primary efficacy endpoints

- Change from baseline in the average daily frequency of moderate to severe VMS, defined as the sum of the number of moderate to severe VMS during 1 week divided by the number of days with data. The daily score here and below are average scores from a 7-day period. Details will be defined in the Statistical Analysis Plan (SAP).
- Change from baseline in the average daily severity score of mild to severe VMS. Baseline VMS severity score is defined as (2xFmo + 3xFse)/(Fmo + Fse), and VMS severity score for a specific week during the double-blind treatment period is defined as (1xFmi + 2xFmo + 3xFse)/(Fmi +Fmo +Fse) where Fmi, Fmo, and Fse are the daily frequencies of mild, moderate, and severe VMS, respectively, during each applicable study week.

Co-primary endpoints will be evaluated at Week 4 and Week 12. See Section 10.3 for definition of baseline.

2.2.2 Secondary efficacy endpoints

- Proportion of responders at Weeks 4 and 12 (i.e., subjects with cutoff number* or greater reduction in the average daily frequency of moderate and severe VMS compared to baseline).
- Time to response, defined as time (in weeks) from randomization to the first time the subject meets responder criteria (i.e., cutoff number* or greater reduction from baseline in the average daily frequency of moderate and severe VMS).

*Note: The cutoff number will be calculated using anchor-based method. The cutoff number is defined as numerical value to maximize the sensitivity and the specificity, using Patient Global Impression of Change (PGIC) as the anchor

- Change from baseline to Weeks 4 and 12 in the Insomnia Severity Index (ISI) total score.

2.2.3 Other efficacy endpoints

- PGIC at Weeks 4 and 12
- Change from baseline to Weeks 4 and 12 in the Pittsburgh Sleep Quality Index (PSQI).
- Change from baseline to Weeks 4 and 12 in the Menopause-Specific Quality of Life (MENQOL) score.
- Change from baseline to Weeks 4 and 12 in the 36-Item Short Form Health Survey (SF-36).
- Change from baseline in the average daily severity score of moderate to severe VMS at Weeks 4 and 12, defined as 2xFmo + 3xFse.

2.2.4 Pharmacokinetic assessments

- Blood samples to assess plasma concentrations of MT-8554 will be performed at 5 visits during the Double-blind Treatment period.

2.2.5 Safety assessments

- Physical examination (including breast safety evaluation)
- Vital signs (blood pressure, pulse, and tympanic body temperature)
- ECG parameters (including cardiac intervals: heart rate, PR, QRS, QT, and QTcF)
- Clinical laboratory assessments (hematology, biochemistry, coagulation, and urinalysis)
- Reproductive hormones (luteinizing hormone [LH], follicle stimulating hormone [FSH], and estradiol [E2])
- Adverse events (AEs)
- Endometrial safety (endometrial thickness, as measured by transvaginal ultrasound, and incidence of endometrial hyperplasia, as measured by endometrial biopsy)
- Depression and anxiety symptoms as measured by 8-item Patient Health Questionnaire (PHQ-8) and 7-Item Generalized Anxiety Disorder questionnaire (GAD7), respectively

3 STUDY DESIGN

3.1 Overall study design

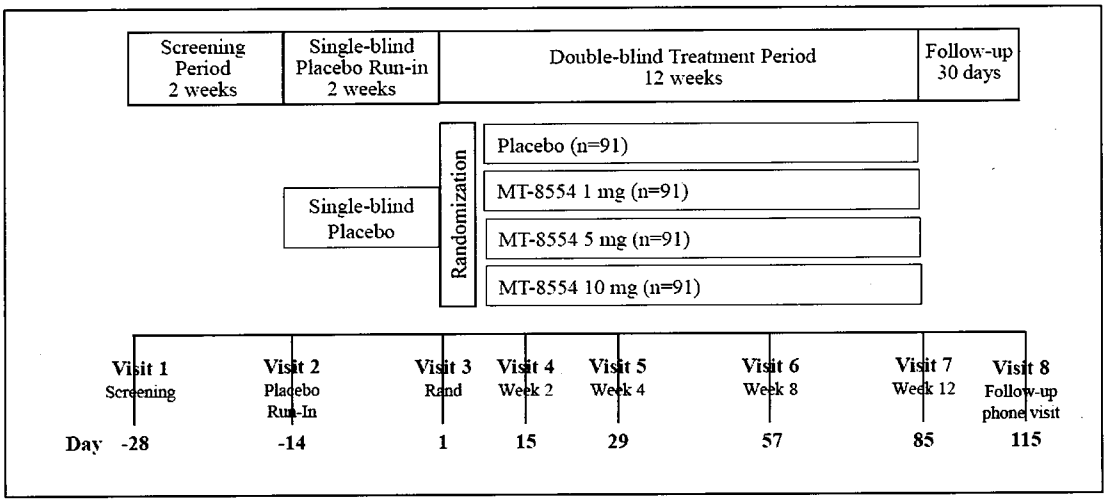
This is a Phase II randomized, double-blind, placebo-controlled study for dose selection.

Subjects meeting eligibility criteria will be enrolled in a 2-week single blind Placebo Run-in period. All eligible subjects will receive single-blind placebo daily before bedtime. Following the Placebo Run-in period, subjects meeting eligibility criteria will enter the 12-week, placebo controlled Double-blind Treatment period. The Double blind Treatment period has 4 arms including: placebo and MT-8554 1, 5, and 10 mg. A single daily dose of study medication will be administered before bedtime. Subjects who complete through Week 12 may be enrolled into the open-label extension (OLE) study (MT-8554-A02) to receive MT-8554 for a further 52 weeks. An End of Study (EOS) Follow-up visit will be conducted by phone for safety follow up 30 days after the end of the Double blind Treatment period for subjects who do not enroll into the OLE study (MT-8554-A02). Total duration is 20 weeks, inclusive of the Screening and Follow up periods (see Figure 1).

A planned interim assessment for safety, and a planned interim analysis for efficacy (futility) and safety will be conducted during the study; enrollment will proceed without interruption.

The primary endpoint will be evaluated at Weeks 4 and 12.

Figure 1 Study Design Schematic



3.2 Rationale for study design

The objectives of this study are to obtain efficacy, safety, and tolerability data for MT-8554 when administered as single doses in post-menopausal women with moderate to severe VMS.

In an attempt to reduce the placebo effect and to ensure the eligibility of subjects, a 2-week single-blind Placebo Run-in period is being conducted. The 12-week Double-blind Treatment period follows the 2003 draft United States (US) Food and Drug Administration (FDA) Guidance for estrogen and estrogen/progestin drug products to treat VMS and vulvar and vaginal atrophy symptoms.

An interim analysis will be conducted to assess futility and safety.

The information obtained from this study will help to determine whether Phase III study is warranted.

Subjective measures (e.g., daily patient diaries) are a valuable means of measuring VMS. 2003 draft FDA guidance recommends subjective measures can be used as primary efficacy endpoints. Therefore, subjective VMS measurements by patient diary will be used in this study as co-primary endpoints.

The Menopausal Strategies: Finding Lasting Answers to Symptoms and Health (MsFLASH) network recommends evaluating comprehensive outcome measures in addition to VMS. The ISI and PSQI are standard sleep-related subjective questionnaires. The MENQOL is a standard QOL questionnaire to assess the impact of menopausal symptoms. The PGIC is a standard subjective questionnaire used for reporting overall improvement.

The data from pharmacokinetic (PK) assessments will be used in combination with those obtained from other clinical studies in a population PK analysis to evaluate PK profiles in subjects with VMS.

3.2.1 Risk:benefit statement

[redacted]

The Sponsor will undertake all reasonable measures, including thorough screening and safety monitoring procedures, to minimize the risk to subjects. [redacted] Additionally, subjects will receive no further dosing if they meet any of the withdrawal criteria listed in Section 4.5.

3.3 Rationale for dose selection

The primary objective of this study is to confirm the efficacy and safety of MT-8554 when administered in post-menopausal women with moderate to severe VMS.

[redacted]

4 SELECTION AND WITHDRAWAL OF SUBJECTS

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

4.1 Number of subjects

Approximately 364 subjects will be randomized in the study, with a target of 91 subjects in each treatment arm.

4.2 Recruitment methods

Subjects will be recruited from referral sites or via media advertisements, if appropriate. All study-specific recruitment material will be approved by the Institutional Review Board (IRB) prior to implementation.

Investigators at referral sites will act as consultants and will be responsible for recruiting patients and performing a first introduction on the aim and course of the clinical study. They will provide source documentation confirming post-menopausal state, as applicable; and clinical symptoms of VMS, including start date, medical history, and concomitant medications.

A sufficient number of subjects will be screened to ensure the planned sample size will be achieved. Each subject will be screened according to the criteria described in Sections 4.3 and 4.4. Only subjects who are eligible for the study will be randomized.

A planned interim assessment for safety, and a planned interim analysis for efficacy (futility) and safety will be conducted during the study; enrollment will proceed without interruption.

4.3 Inclusion criteria

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

1. Provide written informed consent to participate in this study.
2. Subjects must be post-menopausal women who meet at least 1 of the following criteria:
   - Spontaneous amenorrhea for ≥12 months (without an alternative cause)
   - Spontaneous amenorrhea for at least 6 months (without an alternative cause) and with follicle stimulating hormone (FSH) levels >40 mIU/mL (Note: FSH may be retested once within the Screening window for subjects ineligible due solely to this criterion)
   - Documented bilateral salpingo-oophorectomy ≥6 weeks, with or without hysterectomy
   - Total or supracervical (partial) hysterectomy without bilateral salpingo-oophorectomy, and with FSH levels >40 mIU/mL (Note: FSH may be retested once within the Screening window for subjects ineligible due solely to this criterion)

3. Subjects who have 7 or more moderate to severe VMS per day, or 50 or more moderate to severe VMS per week (based upon at least 2 weeks of daily VMS diaries during the Screening period.).
4. Have a consistent bedtime on at least 5 days per week starting at least the week before Screening and expect for the remainder of the study.
5. In the Investigator's opinion, subject is able to understand the nature of the study and any risk involved in participation, and is willing to cooperate and comply with the protocol restrictions and requirements including transvaginal ultrasound and endometrial biopsy.

In addition to the above, for subjects who have participated in the Placebo Run-in period, the following criterion must be met before randomization:

6. Subjects whose mean VMS frequency during the Placebo Run-in period does not drop by more than 50% from the mean level reported for entire duration (at least 2 weeks) of the Screening period.
7. Subjects with >50% of days with VMS diary data entry during each week of the Placebo Run-in period.

4.4 Exclusion criteria

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

1. Subjects with a history of undiagnosed abnormal vaginal bleeding, or any cancer within 5 years except for basal cell carcinoma.
2. Subjects with a history of Hepatitis B, Hepatitis C or HIV.
3. Subjects with a history of psychiatric illness, excessive alcohol intake or use of recreational drugs who are unsuitable for study enrollment and compliance in the opinion of investigator.
4. Subjects exhibiting or with a history of severe adverse reaction or allergy to MT-8554.
5. Subjects exhibiting or with a history of clinically significant lactose intolerance.
6. Subjects with peripheral vascular disease or disorders with associated vasculopathies (i.e. Raynaud's).
7. Subjects with clinically significant conditions which could interfere with the objectives of the study or the safety of the subject, as judged by the Investigator.
8. Subjects with endometrial thickness of ≥5 mm as measured by baseline transvaginal ultrasound performed at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization, assessed locally by the site. (Note: subjects qualifying based on transvaginal ultrasound will proceed to endometrial biopsy)
9. Subjects with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2.0 × upper limit of normal (ULN) above the reference range at

Screening or start of the Placebo-Run in period (Visit 2). (Note: may be retested once within the Screening window for subjects ineligible due solely to these criteria.)

10. Subjects who have received any of the following estrogen or estrogen/progestin containing products: (No washout permitted during the study)
    - 10.1 One week prior to Screening for vaginal hormonal products (rings, creams, gels).
    - 10.2 Four weeks prior to Screening for transdermal estrogen alone or estrogen/progestin products.
    - 10.3 Eight weeks prior to Screening for oral estrogen and/or progestin therapy.
    - 10.4 Eight weeks prior to Screening for intrauterine progestin therapy.
    - 10.5 Three months prior to Screening for progestin implants and estrogen alone injectable drug therapy.
    - 10.6 Six months prior to Screening for estrogen pellet therapy or progestin injectable drug therapy.
11. Subjects who have received any of the following medications within 2 weeks of Screening:
    - 11.1 Use of gabapentin, clonidine, sedatives, or hypnotics.
    - 11.2 Herbal or dietary supplements, including black cohosh, soy, phytoestrogens or over the counter agents known to possibly have an effect on VMS.
12. Subjects who have received any of the following medications within 7 days prior to the start of Placebo Run-in period (Visit 2):
    - 12.1 [redacted]
    - 12.2 Any other medication that could potentially interfere with the study procedures or compromise safety as judged by the Investigator.
13. Treatment with antidepressants which either initiated or required dose adjustments within 6 months of Screening. Subjects with antidepressants prescribed for the treatment of VMS and those using paroxetine will be excluded.
14. Subjects of childbearing potential.
15. Subjects who have participated in any study with an investigational study medication within 12 weeks (or, if relevant, 5 half-lives of that study medication, whichever is the longer) prior to the start of Placebo Run in period (Visit 2).
16. Subjects with an abnormal (pre-defined histological categories)* result from baseline endometrial biopsy performed at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization. Subjects with insufficient tissue for diagnosis will not be qualified. (Note: Subjects with insufficient tissue for diagnosis may be retested once within the time window.)
    *Note: The histological categories are based on 2003 draft FDA guidance.

Note: No study waiver will be granted.

4.5 Withdrawal of individual subjects

4.5.1 Discontinuation from study treatment

Investigators may choose to temporarily or permanently discontinue study treatment for any reason, including AEs or tolerability. [redacted] Study drug administration can be interrupted and reinitiated following up to 7 days of discontinuation. An unscheduled study visit can be used to reassess subject's symptoms and willingness to reinitiate study drug. In these circumstances, the patient will complete the dosing through the remainder of the planned study duration. If treatment is discontinued, and patient is not willing to resume study medication, every effort should be made to continue the subject on study, e.g., attending study visits and carrying out study procedures through to the final visit. For subjects decline continuing on the study, see Section 4.5.2.

The suspension interval (start and end dates of suspension) and reason for suspending treatment must be recorded in source documents and the electronic Data Collection Form (eCRF).

Subjects who become pregnant during the study should be withdrawn from study treatment. Also see Section 8.9 for necessary documentation and procedures for following up with the subject.

4.5.2 Discontinuation from study

Subjects may withdraw from the study for any reason. The Investigator will discontinue a subject from the study if ANY of the following criteria are met:

- The subject wishes to voluntarily withdrawal from the study
- The subject is lost to follow-up
- The subject who experiences elevated ALT or AST >3 × ULN and a total bilirubin >2 × ULN (such subjects should be treated per standard of care and followed till resolution.)
- The subject has an abnormal baseline endometrial biopsy result, as assessed by the endometrial biopsy adjudication committee.
- The subject has an abnormal result from an endometrial biopsy conducted at any time during the study based on Investigator's judgement (The biopsy report or slides may be requested for central assessment).
- The subject has endometrial thickness of ≥5 mm as measured by transvaginal ultrasound conducted at any time during the study based on Investigator's judgement (The images may be requested for central assessment).
- Continuing the subject in the study off treatment would be detrimental to the subject's safety in the opinion of the Investigator

If a subject is discontinued prematurely from the study, the date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the eCRF.

In case of discontinuation from study, the EOT visit assessments should be performed, as far as possible (Sections 5.2.3.5 and 5.2.4) and any unresolved AEs or SAEs will be followed up according to Section 8.10.

The Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation 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 EOS assessments.

Subjects withdrawn from the study following randomization may not re-enter the study.

4.6 Study stopping criteria

4.6.1 Stopping criteria

The study may be terminated by the sponsor at any time upon becoming aware of data that could compromise the safety and/or wellbeing of subject or for any other reason it deems appropriate.

4.7 Lifestyle restrictions

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

4.7.1 Alcohol restrictions

Subjects are prohibited from excessive consumption of food or drink containing alcohol (>2 units* per day) at all other times from the Screening visit through the Follow-up visit.
*Note: 1 unit of alcohol is equivalent to 8 g of pure alcohol.

4.7.2 Caffeine and xanthines

Subjects should avoid excessive consumption or increase in consumption from baseline 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 through the Follow-up visit. (Increased xanthines intake can interfere with assessment of sleep quality)

4.7.3 Contraception

Women of childbearing potential are excluded from this study; therefore, contraception is not required.

4.7.4 Diet

Subjects will be required to fast (except for water) for 6 hours after dosing at the night prior to study visits.

5 STUDY PLAN

Study assessments are summarized in the Schedule of Assessments (Table 1).

Table 1 Schedule of Assessments

Study Period	Screening	Placebo Run-in	Double-blind Treatment					Follow-up
Visit Number	Visit 1	Visit 2	Visit 3 (Randomization)	Visit 4	Visit 5	Visit 6	Visit 7 (EOT)	Visit 8 (EOS)
Study Week	Week -5 to -4	Week -2		Week 2	Week 4	Week 8	Week 12[8]	Week 16[9]
Study Day ±Window	Day -35 to -28	Day -14±3	Day 1	Day 15 ±3	Day 29 ±3	Day 57 ±3	Day 85 ±3	Day 115 ±3
Informed consent	X							
Demography and height	X							
Medical/drug/smoking/alcohol/surgical history	X	X	X					
Inclusion/exclusion criteria	X[1]	X	X					
Physical examination[2] Complete (C) or Routine(R)	C	R	R	R	R	R	R	
Breast examination	X		X				X	
Body weight	X		X				X	
Vital signs	X	X	X	X	X	X	X	
12-lead ECG	X		X				X	
Transvaginal ultrasound[4]	X[10]						X	
Endometrial biopsy[4]	X[10]						X	
Routine lab tests	X[1]	X	X	X	X	X	X	
Reproductive hormones (FSH, LH, E2)	X[1]		X				X	
VMS diary[5]	←						→	
ISI, MENQOL, PSQI, and SF-36		X	X		X		X	
PGIC					X		X	
PHQ-8 and GAD7		X	X	X	X	X	X	
Dispensing single-blind placebo[6]		X						
Dispensing MT-8554 /Placebo[6]			X	X	X	X		
Drug accountability			X	X	X	X	X	

Study Period	Screening	Placebo Run-in	Double-blind Treatment					Follow-up
Visit Number	Visit 1	Visit 2	Visit 3 (Randomization)	Visit 4	Visit 5	Visit 6	Visit 7 (EOT)	Visit 8 (EOS)
Study Week	Week -5 to -4	Week -2		Week 2	Week 4	Week 8	Week 12[8]	Week 16[9]
Study Day ±Window	Day -35 to -28	Day -14±3	Day 1	Day 15 ±3	Day 29 ±3	Day 57 ±3	Day 85 ±3	Day 115 ±3
Blood for MT-8554 PK[7]			X	X	X	X	X	
Adverse events	←							→
Concomitant medication	←							→
Compliance [redacted] Calls to Subjects[11]		←					→	

Abbreviations: E2=estradiol; ECG=Electrocardiogram; EOS=End of Study; EOT=End of Treatment Visit; FSH=Follicle stimulating hormone; FU=Follow-up Visit; ISI=Insomnia Severity Index; GAD7=Generalized Anxiety Disorder-7 questionnaire; LH=luteinizing hormone; MENQOL=Menopause-Specific Quality of Life; PGIC=Patient Global Impression of Change; PHQ-8=Eight-Item Patient Health Questionnaire; PK=Pharmacokinetics; PSQI=Pittsburgh Sleep Quality Index; SF-36=36-Item Short Form Health Survey; VMS=Vasomotor symptoms.

1. FSH and/or liver function labs may be retested once within the Screening window for subjects who are ineligible due solely to inclusion/exclusion criteria related to these tests.
2. Physical examination:
   a. Complete: abdominal, cardiovascular, general appearance, head, eyes, ears/nose/throat, lymph nodes, musculoskeletal, neck, neurological, dermatological, respiratory and other.
   b. Routine: abdominal, cardiovascular, general appearance, respiratory and other.
3. Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature) will be measured at all visits.
4. Transvaginal ultrasound and endometrial biopsy to be performed only on subjects who have a uterus. Pelvic examination will be performed only with endometrial biopsy.
5. VMS diary data will be collected daily for the entire duration (est. 14-days) of Screening and Placebo Run-in period for eligibility determination. Subjects are to be instructed to complete the daily diary each day without interruption for the entire duration of the study through Week 12.
6. Investigator should instruct subject to administer dose at least 2 hours after starting the evening meal and approximately 30 minutes before bedtime.
7. Blood samples for MT-8554 PK will be collected at Visits 3 through 7. Date and time of most recent dose will be recorded at Visits 4 through 7.
8. The EOT should be performed for subjects who complete as well as those who withdraw from the study early.
9. The Follow-up visit will be conducted by phone 30 days after the EOT visit for subjects who complete as well as those who withdraw early from the study. The Follow-up visit should not be done for subjects enrolling in the long-term extension study, should it be implemented.
10. Baseline assessments for transvaginal ultrasound and endometrial biopsy at baseline may be scheduled and conducted at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization, to accommodate site specific scheduling. Note: subjects qualifying based on transvaginal ultrasound will proceed to endometrial biopsy.
11. Site staff will make periodic calls to the subjects at a minimum during weeks where no in clinic visits occur, to confirm compliance with daily VMS diary data entry [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.

There is no washout permitted during the study.

5.2 Description of study phases

5.2.1 Screening (Visit 1)

Screening assessments will be performed from Week -5 to Week -4, inclusive, where eligibility for the study will be assessed. Subjects will be requested to attend the clinic after a 6-hour fasting period (apart from water).

Re-screening will be allowed once in the study for subjects who do not meet the screening criteria with the exception of;

- Inclusion criteria #3
- Exclusion criteria #8
- Exclusion criteria #16

All screening assessments will be performed again – with the exception of transvaginal ultrasound and endometrial biopsy; if baseline transvaginal ultrasound and endometrial biopsy are performed within 3 months of re-screening, repeated assessments will not be required.

Written informed consent will be obtained before any screening procedures are performed. The following assessments will be performed (refer to Table 1 for further details):

- Written informed consent
- Inclusion/exclusion criteria
- Demography
- Medical, drug, smoking, alcohol, and surgical history
- Physical examination (complete; see Section 6.7.1)
- Breast examination
- Height and weight
- 12-lead ECG
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis) Note: Liver function labs may be retested once within the Screening window for subjects who are ineligible due solely to exclusion criteria #9
- Reproductive hormone assessments: E2, LH, and FSH (Note: FSH may be retested once within the Screening window for subjects who are ineligible due solely to inclusion criteria #2)
- Transvaginal ultrasound and endometrial biopsy for subjects with a uterus

  - Note: Baseline assessments for transvaginal ultrasound and endometrial biopsy will be performed at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization.
  - Note: Subjects qualifying based on transvaginal ultrasound will proceed to endometrial biopsy (see exclusion criteria #8).
  - Note: Subjects with insufficient tissue for diagnosis at baseline endometrial biopsy may be retested once within the time window (see exclusion criteria #16).
- Provide VMS diary and educate subject in its use
- AE and prior/concomitant medication recording

5.2.2 Placebo Run-in (Visit 2)

Subjects determined to be eligible based on Screening data will participate in a 2-week Placebo Run-in period beginning at Week -2. Subjects will be requested to attend the clinic after a 10-hour fasting period (apart from water).

The following assessments will be performed (refer to Table 1 for further details):

- Verify inclusion/exclusion criteria
- Verify demography and medical/drug/smoking/alcohol/surgical history
- Physical examination (routine; see Section 6.7.1)
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Transvaginal ultrasound and endometrial biopsy for subjects with a uterus
  - Note: Baseline assessments for transvaginal ultrasound and endometrial biopsy will be performed at any time during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization.
  - Note: Subjects qualifying based on transvaginal ultrasound will proceed to endometrial biopsy (see exclusion criteria #8).
  - Note: Subjects with insufficient tissue for diagnosis at baseline endometrial biopsy may be retested once within the time window (see exclusion criteria #16).
- Review VMS diary (re-educate subject if necessary)
- Questionnaires: ISI, MENQOL, PSQI, SF-36, PHQ-8, and GAD7
- Dispense single-blind placebo
- AE and prior/concomitant medication recording

5.2.3 Double-blind Treatment (Visits 3 through 7)

Subjects who successfully complete Screening and Placebo Run-in periods will return to the clinic for the Randomization visit on Day 1 and participate in the Double-blind Treatment period.

Inclusion and exclusion criteria will be reviewed to confirm eligibility prior to randomization.

Randomized subjects who are withdrawn early from the study should, where possible, complete the procedures scheduled for the EOT (Week 12) visit as soon as possible after withdrawal. Every effort should be made to maintain randomized subjects on study, even in cases where treatment has been discontinued.

5.2.3.1 Randomization (Visit 3)

The following assessments will be performed prior to randomization (refer to Table 1 for further details):

- Verify inclusion/exclusion criteria prior to randomization
- Physical examination (routine; see Section 6.7.1; including weight)
- Breast examination
- 12-lead ECG
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Reproductive hormone assessments: E2, LH, and FSH
- Review VMS diary (re-educate subject if necessary)
- Questionnaires: ISI, MENQOL, PSQI, SF-36, PHQ-8, and GAD7
- Blood sample for MT-8554 PK
- Perform study medication accountability
- Dispense study medication
- AE and prior/concomitant medication recording
- [redacted]

5.2.3.2 Week 2 (Visit 4)

- Physical examination (routine; see Section 6.7.1)
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Review VMS diary (re-educate subject if necessary)
- Questionnaires: PHQ-8 and GAD7
- Blood sample for MT-8554 PK (record most recent dose date and time)
- Perform study medication accountability
- Dispense new study medication
- AE and prior/concomitant medication recording
- Diary compliance [redacted] during Week 3

5.2.3.3 Week 4 (Visit 5)

- Physical examination (routine; see Section 6.7.1)
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)

- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Review VMS diary (re-educate subject if necessary)
- Questionnaires: ISI, MENQOL, PGIC, PSQI, SF-36, PHQ-8, and GAD7
- Blood sample for MT-8554 PK (record most recent dose date and time)
- Perform study medication accountability
- Dispense new study medication
- AE and prior/concomitant medication recording
- Diary compliance [redacted] during Weeks 6 and 7

5.2.3.4 Week 8 (Visit 6)

- Physical examination (routine; see Section 6.7.1)
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Review VMS diary (re-educate subject if necessary)
- Questionnaires: PHQ-8 and GAD7
- Blood sample for MT-8554 PK (record most recent dose date and time)
- Perform study medication accountability
- Dispense new study medication
- AE and concomitant medication recording
- Diary compliance [redacted] during Weeks 9, 10 and 11

5.2.3.5 Week 12 or early termination (Visit 7; EOT)

- Physical examination (routine; see Section 6.7.1; including weight)
- Breast examination
- 12-lead ECG
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Reproductive hormone assessments: E2, LH, and FSH
- Transvaginal ultrasound and endometrial biopsy (for subjects with a uterus)
- VMS diary collection
- Questionnaires: ISI, MENQOL, PGIC, PSQI, SF-36, PHQ-8, and GAD7
- Blood sample for MT-8554 PK (record most recent dose date and time)
- Perform study medication accountability
- AE and prior/concomitant medication recording

Subjects who complete through Week 12 may be enrolled into the OLE study (MT-8554-A02) to receive MT-8554 for a further 52 weeks.

5.2.4 Follow-up (Week 16; Visit 8; EOS)

Subjects who do not enroll into the OLE study (MT-8554-A02) will be telephoned by the Investigator (or designee) 30 days after EOT, for a Follow-up visit. Information on any new AEs, follow-up on existing AEs, and prior/concomitant medication will be recorded.

5.2.5 Post-study access to treatment

MT-8554 will not continue to be available to subjects following completion or termination of the study, in accordance with the study information given to the subjects.

5.2.6 Reminder Phone Calls to Subject

Site will make periodic calls to subjects at a minimum during weeks where no in clinic visits occur, to ensure subject compliance with daily VMS diary completion [redacted]. AEs reported during the calls will be documented as applicable.

5.2.7 Unscheduled visits

An unscheduled visit is defined as any visit to the Investigator site outside of the Protocol specified study site visits due to safety reasons or when a repeat test and/or 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 Schedule of Assessments (Table 1). A priority order will be in effect when more than 1 assessment is required at a particular time point and this will be described in a separate document. Time windows for relevant assessments will also be described in a separate document.

6.1 Informed consent form

The Investigator or designee will fully explain the nature of the study to subjects using the IRB-approved informed consent document. When the subject agrees to participate in the study, the subject must voluntarily sign a consent form prior to the initiation of any study procedures. A copy of the signed and dated informed consent document will be given to the subject. The signed and dated original consent form will be retained by the Investigator. Informed consent will be obtained from all subjects. A subject cannot be entered into the study until he/she has signed and dated the consent form.

The Investigator or designee is responsible for ensuring that the subject understands the risks and benefits of participating in the study, including answering any questions the subject may have throughout the study and sharing any new information in a timely manner that may be relevant to the subject's willingness to continue his/her participation in the study.

6.2 Demography

The following subject characteristics will be recorded at Screening: date of birth, sex, weight, height, and race.

6.3 Medical and surgical history

Medical, drug, smoking, alcohol, and surgical history will be recorded. Medical/surgical history includes any medical condition or surgical history prior to Screening.

6.4 Prior and concomitant medication

Prior medications are defined as any medication taken prior to the double-blind treatment period.

Any prior medication, including prescription and over-the-counter medications, taken within 1 month prior to Screening will be recorded on the eCRF. Information recorded will include: name of drug, dose, duration of use, and reason for use.

Concomitant medication is defined as any medication, other than study medication, which is taken during the study, including prescription and over-the-counter medications. All concomitant medications taken while the subject is participating in the study will be recorded.

Concomitant medication will be given only if deemed necessary by the Investigator or the subject's personal physician.

6.4.1 Prohibited medication

Subjects must not participate in any other clinical study involving administration of another investigational study medication from Screening through the final Follow-up visit.

[redacted]

Subjects must not take any prescribed or non-prescribed systemic or topical medication (including herbal or dietary supplements) known to possibly have an effect on VMS or sleep during the study. Such drugs include, but not limited to estrogen, gabapentin, clonidine, progestin, black cohosh, soy, phytoestrogens, sedatives, and hypnotics.

Antidepressants prescribed for the treatment of VMS and paroxetine are prohibited during the study period. Other antidepressants are permitted as long as the doses are stable for 6 months or more prior to Screening and no dose adjustments are anticipated during the study period.

6.4.2 Rescue medication

There is no known antidote to MT-8554. In the case of significant AEs, appropriate medical management will be provided by site staff.

6.5 Efficacy assessments

6.5.1 Subjective vasomotor symptoms

Subjects will be asked to record frequency and severity of VMS in an electronic diary beginning at Randomization (Day 1) and throughout the Double-blind Treatment period. To assess eligibility, subjects will also be asked to complete the diary for 14 days each during the Screening and Placebo Run-in periods. See APPENDIX 1 for an example of the VMS diary.

VMS diaries will be provided by the Sponsor and given to subjects by clinic personnel, with instructions on its use. A paper back-up VMS diary card will be used in case of device malfunction, stolen or lost. See Section 9.1 for further information related to VMS diary data collection and transfer.

Definitions of VMS severity levels (per 2003 draft FDA guidance) are provided in Table 2.

Table 2 VMS Severity Levels

Severity	Definition
Mild	Sensation of heat without sweating
Moderate	Sensation of heat with sweating, able to continue activity
Severe	Sensation of heat with sweating, causing cessation of activity

Abbreviations: VMS=vasomotor symptoms

6.5.2 Subject questionnaires

6.5.2.1 Menopause-Specific Quality of Life[6]

The MENQOL is self-administered and consists of a total of 29 items in a Likert-scale format. Each item assesses the impact of 1 of 4 domains of menopausal symptoms, as experienced over the last month: vasomotor (items 1–3), psychosocial (items 4–10), physical (items 11–26), and sexual (items 27–29). Items pertaining to a specific symptom are rated as present or not present, and if present, how bothersome on a 0 (not bothersome) to 6 (extremely bothersome) scale. Means are computed for each subscale by dividing the sum of the domain's items by the number of items within that domain. Non-endorsement of an item is scored a "1" and endorsement a "2," plus the number of the particular rating, so that the possible score on any item ranges from 1 to 8. See APPENDIX 2 for an example of the MSQOL.

6.5.2.2 Insomnia Severity Index[7]

The ISI is a self-rated, 7-item questionnaire designed to measure a subject's current perception of symptom severity, distress, and daytime impairment. Items include: the severity of sleep onset and maintenance (middle and early morning awakening) difficulties, satisfaction with current sleep pattern, interference with daily functioning, appearance of impairment attributed to the sleep problem, and the degree of concern caused by insomnia. See APPENDIX 3 for an example of the ISI.

6.5.2.3 Pittsburgh Sleep Quality Index[8]

The PSQI is a self-rated questionnaire which assesses sleep quality and disturbances. Nineteen individual items generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Scoring of the answers is based on a 0 to 3 scale, whereby 3 reflects the negative extreme on the Likert Scale. The sum of scores of the 7 component scores yields 1 global score. A global sum of 5 or greater indicates a "poor" sleeper. See APPENDIX 4 for an example of the PSQI.

6.5.2.4 36-Item Short Form Health Survey[9]

The SF-36 is a self-rated questionnaire which assess 8 health concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. In addition, it includes a single item that provides an indication of perceived change in health. See APPENDIX 5 for an example of the SF-36.

6.5.2.5 Patient Global Impression of Change[10]

The PGIC is used to assess the subject's rating of overall improvement. Subjects rate their perceived change on a 7-point scale from 'very much improved' to 'very much worse'. See APPENDIX 6 for an example of the PGIC.

If necessary, further details will be provided in a separate study reference manual.

6.6 Pharmacokinetic assessments

Blood samples will be collected via cannulation or direct venipuncture in a suitable forearm vein. The actual date and time of each blood sample and the most recent dose date and time will be recorded in the source documents and eCRF.

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

Sample handling details will be described fully in a separate document. At agreed time points, samples will be sent frozen (packed in dry ice) by courier from the clinic to the lab. Contingency samples will be shipped separately to the primary samples.

Samples will be analyzed using standard methods.

6.7 Safety assessments

Please refer to Section 8 for details of AE management.

6.7.1 Physical examination

The complete 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'.

The routine physical examination will consist of a routine assessment of the following body systems: abdominal, cardiovascular, general appearance, respiratory and 'other'.

6.7.2 Breast examination

A breast examination (symmetry of breast shape, contour of breast, appearance of skin, nipple, areola, lymph nodes status, presence and characterization of lesions) will be performed at Screening, Visits 3 and 7. The Investigator or designated study staff will perform a clinical examination and record in the eCRF.

6.7.3 Vital signs

Subjects' vital signs (sitting blood pressure, pulse, and tympanic body temperature) will be taken at each visit. Subjects will undergo an assessment of blood pressure at each visit using a blood pressure recording device with an appropriate cuff size and with the subject in a sitting position. The same arm will be used for all measurements. Pulse rate and tympanic body temperature will also be measured. An infrared ear thermometer will be used to measure tympanic body temperature.

The Investigator will perform an overall evaluation of vital signs 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 for abnormal results.

6.7.4 Electrocardiogram

A 12-lead ECG will be performed after the subject has rested for at least 5 minutes in the supine position. The Investigator will perform an overall evaluation of the ECG results 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 for abnormal results.

6.7.5 Transvaginal ultrasound

For subjects who have a uterus, a transvaginal ultrasound will be performed at baseline during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization, and Week 12 or early termination to measure endometrial thickness. The scans will be performed locally by qualified personnel and a blinded review will be conducted centrally. The Investigator will read the scan at baseline and judge exclusion criterion #8. Procedures for the handling of these assessments will be described in full in separate documents.

6.7.6 Endometrial biopsy

For subjects who have a uterus, and qualify for the enrollment based on the transvaginal ultrasound (exclusion criteria #8), an endometrial biopsy will be performed at baseline during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization, and Week 12 or early termination to assess endometrial hyperplasia. The biopsy samples will be processed and assessed by central laboratory. Biopsy results will be adjudicated by a committee consisting of 3 independent expert pathologists, who will remain blinded. Procedures for the handling of these assessments and adjudications will be described in full in separate documents.

Pelvic examination will be performed only with the endometrial biopsy at baseline during the Screening period or the Placebo Run-in period, but at least 7 days prior to randomization, and Week 12 or early termination.

6.7.7 Routine laboratory evaluations

Blood and urine samples will be collected for routine clinical laboratory safety evaluations according to Table 1. The laboratory safety evaluations performed during the study are presented in Table 3.

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 Trial Master File.

The Investigator will perform a clinical assessment of all laboratory data. The Investigator will record the assessment as 'normal', 'abnormal CS', or 'abnormal NCS'. Lab test abnormalities of clinical significance will be reported as AEs. Repeat lab tests or measurements will be performed for abnormal results.

Table 3 Routine Laboratory Evaluations

Hematology:	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin 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	Estradiol[1]
Bilirubin (direct and total)	Luteinizing hormone[1]
Coagulation:	
Prothrombin time	Activated partial thromboplastin time
International normalized ratio	
Urinalysis:	
Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood	
Microscopic examination[2]	

[1] Screening, Week 1, and Week 12 only.
[2] Performed only if required, based on urinalysis results.

Blood and urine samples will be analyzed by [redacted] using standard methods. Procedures for the handling of samples will be described in full in a separate document.

6.8 Screening and safety-related questionnaires

6.8.1 Eight-Item Patient Health Questionnaire[11]

The PHQ-8 is a self-rated questionnaire assessing current depressive symptoms based on 8 out of 9 criteria of the DSM-IV. See APPENDIX 7 for an example of the PHQ-8.

6.8.2 Generalized Anxiety Disorder-7[12]

The GAD7 is a self-rated questionnaire assessing current anxiety levels. See APPENDIX 8 for an example of the GAD7.

7 STUDY MEDICATIONS, TREATMENT AND DOSING REGIMEN

7.1 Investigational medicinal product

7.1.1 Drug product

MT-8554 capsules and matching placebo are white capsules with no identifying mark. MT-8554 capsules contain [redacted] mg, or [redacted] mg of MT-8554 drug substance per capsule.

Bulk capsules will be packed in double polyethylene bag in stainless steel drum. Individual subject doses will be packed in blister wallets, labeled, and QP certified by [redacted].

MT-8554 and matching placebo capsules are manufactured, tested, and released according to Good Manufacturing Practice. All labeling will comply with applicable regulatory requirements. The Sponsor will provide the necessary documentation, such as a Certificate of Analysis or Quality Control release document.

7.1.2 Study drug supply

The Sponsor will provide MT-8554 to each site for each subject for the duration of their participation in the study. The Investigator, Study Nurse, or hospital pharmacy will dispense MT-8554 capsules at study visits according to protocol. A sufficient quantity of the appropriate strength MT-8554 capsules ([redacted] mg, [redacted] mg, and placebo) will be dispensed consistent with each subject's daily dosage requirement. Subjects should be instructed to bring their study medications with them to each visit and the Investigator or Study Nurse will perform a capsule count to ensure the subject has a sufficient supply of medication to last until the next scheduled visit. Subjects must return all study drugs remaining in their possession to study staff at the Week 12 visit.

7.1.3 Formulation, packaging, site storage, and labeling (MT-8554)

Capsules will be provided in [redacted]. Study drug will be provided to the study sites [redacted] and should be stored according to the investigational medicinal product (IMP) clinical label.

MT-8554 capsules must be dispensed [redacted]. Subjects will be instructed to store the medication per the IMP clinical label.

Documentation for MT-8554 capsules will include, but may not be limited to, the following information:

- Receipt date
- Description of drug package, and drug product
- Lot/Batch/Code/other
- Expiration and Manufacturing dates
- Dispensing information
- IND number
- Certificate of Compliance

7.1.4 Shipping, receipt, handling and storage

On receiving a shipment of finished study medication at the Investigator site, the Investigator or designee will conduct an inventory check and complete a supplies receipt document, the original of which will be retained at the Investigator site; a copy must be returned to the Sponsor or designee. The Investigator or designee will maintain a record of all study medication received and returned.

Study medication at the Investigator site will be stored according to the conditions stated on the IMP clinical label in a locked, restricted-access area. A temperature log recording the daily continuous temperature of the storage area will be maintained (including weekends). Any study medication storage temperature deviations will be reported to the Sponsor.

7.1.5 Dispensing

At each visit, the Investigator or designee will provide the subject with the allocated dose. A record of the study medication dispensed to each subject will be maintained by the Investigator or designee in a Drug Accountability Log. Any opened wallets will not be re-dispensed.

7.1.6 Study drug accountability

The Investigator or designee must maintain an accurate record of the shipment and dispensing of study drug in a Drug Accountability Log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Subjects will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

7.1.7 Disposal and destruction

At study close-out, and as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed Drug Accountability Log to the Sponsor's designated monitor or to the address provided in the Investigator Binder at each site.

The study drug supply may only be destroyed at the designated Sponsor facility or third party, as appropriate.

7.2 Dosing

Subjects are to self-administer study medication once daily before bedtime.

MT-8554 and placebo capsules should be swallowed whole with approximately 8 oz of water (subjects may drink an additional 8 oz of water if they have difficulty swallowing the capsules). The capsules must not be chewed, crushed or divided.

7.3 Compliance

The prescribed dosage, timing and mode of administration of study medication may not be changed. Subjects will be asked questions regarding the compliance, any departures from the intended regimen must be recorded in the eCRF.

Study medication accountability and subject compliance will be documented throughout the Placebo Run-in and Double-blind Treatment periods using study medication dispensing and return record forms. For Subjects who do not return their medication cards, the site will question them to determine compliance.

Subjects will be asked to return all unused medication including empty and partially used wallets. Study medication dispensed at the previous visit will be retrieved by the Investigator.

Non-compliance is defined as taking [redacted] of study medication during any evaluation period (visit to visit).

7.4 Subject identification

Each subject will be assigned a unique Subject Number at the Screening visit. At the point of randomization, each subject will receive a unique Randomization Number. Both the Subject Number and the Randomization Number will be documented in the subject's source documents. The Subject Number will be used to identify subjects in the study.

Re-screened subjects will be assigned a new Subject Number.

A list identifying the subjects by their Subject and Randomization Numbers will be kept at the Investigator site.

7.5 Procedures for assigning subjects to treatment groups

Randomization will take place after confirmation of inclusion/exclusion criteria prior to dispensing the first study medication on Day 1. Subjects will be randomly allocated on a 1:1:1:1 basis to 1 of 4 treatments (Section 3.1). Subjects will be randomized with IVRS/IWRS system.

7.6 Maintenance of the study blind and unblinding

In the single-blind Placebo Run-in period, Investigator site personnel will know that the study medication is placebo; however, subjects will not.

During the Double-blind Treatment period, neither the subject nor Investigator site personnel will know which treatment is being taken. Each subject's treatment will be given a unique code number, traceable to the identity, dose and batch number of the study medication. The IVRS/IWRS system will be used to hold treatment codes for each subject. The codes will only be accessible to authorized IVRS/IWRS users.

The IVRS/IWRS should not be accessed to break the treatment code for reasons other than safety or in an emergency. Should the Investigator wish to break the code for such reasons, he/she should consult the Sponsor (or designee) in advance. If this is not possible, the Investigator may access the IVRS/IWRS to obtain the treatment code and provide the system with the reason for breaking the blind. 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).

Because PK analysis will only be performed on samples from subjects receiving active drug, unblinded randomization codes will be given to PK lab.

An electronic list of randomization codes will be retrieved from IVRS/IWRS and transferred to the Sponsor at the end of the study.

MT-8554 and placebo are identical in appearance and will be packaged identically and suitably labeled 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 Safety Follow-up period (30 days after the last treatment visit) will be recorded in the eCRF. Even if the AE is assessed by the Investigator as not related to study medication, its occurrence must be recorded in the source documents and eCRF. AEs will be classified as 'baseline' if they occur before the administration of study medication.

AEs will be classified as 'treatment-emergent' if they arise following the first administration of study medication in the Double-blind Treatment period (after randomization) or if a pre-dose AE increases in severity following the first administration of study medication in the Double-blind Treatment period (after randomization).

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 any untoward medical occurrence in a subject 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 unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of study medication, whether or not considered related to the study medication.

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 hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is a medically important condition.

Medical and scientific judgment 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 hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 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 hospitalization, 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 hospitalization (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 hospitalization.

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 study medication

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

Reasonable Possibility – The relationship of the clinical event to the study medication 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 study medication 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

8.5.1 Clinical laboratory abnormalities

The Investigator will exercise medical judgment in deciding whether abnormal laboratory test results are clinically significant. Laboratory abnormalities which are judged by the Investigator to be clinically significant will be recorded as AEs.

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

All 'abnormal CS' laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant. Repeat laboratory tests or measurements will be performed for abnormal results.

8.6 Recording and reporting of adverse events

All AEs, regardless of the relationship to study medication, occurring from the time written informed consent is obtained from a subject through the EOS/Follow-up visit or subject early withdrawal from the study, and any AEs or SAEs reported spontaneously through the end of the Safety Follow-up period, should be reported to the Sponsor or designee.

NOTE: Elective hospitalization or procedure/surgery planned before subject enrollment for a preexisting medical condition does not constitute an AE unless the underlying disease or condition worsens after signing informed consent.

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.

All AEs will be recorded in the source documents and AE eCRF. The AE eCRF should contain a description of the event, date of onset, date of resolution, severity, treatment required, relationship to study medication, action taken with the study medication, 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 study medication (as defined in Section 8.4).

Pre-existing illnesses, which started prior to study 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 study medication related after the Safety Follow-up period, then they must notify the Sponsor or the designee 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 reported to the Sponsor or the designee using the ***Serious Adverse Event (SAE) Form in Clinical Study*** **within 24 hours** of the Investigator becoming aware of the SAE. All SAEs must also be entered in the AE section of the eCRF **within 24 hours.**

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 designee reporting contact for SAEs is as follows:

Email: [redacted]

Fax: [redacted]

In case of any email problems, the SAE form will be sent to the Sponsor via email or fax to:

E-mail: [redacted]

Fax: [redacted]

Reports of pregnancy, although <u>not</u> classified as an SAE, will be handled and reported as in Section 8.9.

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 central IRB(s). The Investigator will be responsible for

informing the local IRB(s) of relevant safety information, including SUSARs, as per local laws and requirements.

8.8 Adverse events associated with endometrial safety assessments

A transvaginal ultrasound and endometrial biopsy will be performed for subjects with a uterus. These procedures will be performed to assess endometrial safety (endometrial thickness, as measured by transvaginal ultrasound, and incidence of endometrial hyperplasia, as measured by endometrial biopsy). The scans by ultrasound will be processed and assessed centrally. Biopsy samples will be processed and assessed by central laboratories. Biopsy results will be adjudicated by a committee consisting of 3 independent expert pathologists.

The Investigator will perform an overall evaluation of the transvaginal ultrasound results and endometrial biopsy report. The Investigator will exercise medical judgment in deciding whether abnormal results are clinically significant. Abnormalities which are judged by the Investigator to be clinically significant will be recorded as AEs.

If a subject has an abnormal endometrial stripe of ≥5 mm thickness as measured by transvaginal ultrasound performed at Week 12 or early termination, independent of the results of endometrial biopsy, the Investigator will be informed and advised to refer subject to a gynecologist for further management. Further management and the decision to conduct a hysteroscopy and dilatation/curettage will be deferred to the physician's opinion and the subject's acceptance.

8.9 Pregnancy

If a female subject who has been exposed to the study medication becomes pregnant, the course and outcome of the pregnancy should be monitored and documented.

Pregnancy occurring in a female subject who has been exposed to the study medication, although not classified as an SAE, must be reported using the same timelines and contact details as an SAE (Section 8.7) via a paper ***Pregnancy Notification Form in Clinical Study*** form. If the outcome or course of the pregnancy involves an SAE (e.g., a congenital anomaly or spontaneous abortion), then the ***Serious Adverse Event (SAE) Form in Clinical Study*** needs to be completed.

Subjects who become pregnant while on study should be withdrawn from treatment, as described in Section 4.5.1.

8.10 Follow up of adverse events

The Investigator should follow up with subjects who experienced AEs/SAEs, until the event has resolved or stabilized, any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed. In the event of death, if possible, a full pathology report should be supplied.

8.11 Reference safety information

The reference safety information for this clinical study is the MT-8554 Investigator's Brochure[2].

8.12 Overdose

There is no known antidote for MT-8554. Any signs or symptoms of a possible overdose will be treated supportively. In the case of an emergency, standard emergency procedures and medical care will be given.

If the subject takes a dose which is greater or more frequent than that specified in the Protocol (with or without associated symptoms), this overdose is an AE and must be reported to the Sponsor or the designee on the AE eCRF.

If the overdose meets serious criteria, the SAE must be reported to Sponsor or the designee immediately or within 24 hours of awareness using the ***Serious Adverse Event (SAE) Form in Clinical Study*** according to SAE reporting procedures (see 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 eCRF 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.

Subjects will record the occurrence and severity of VMS on an ongoing basis using a VMS diary, which includes an electronic patient-reported outcome (PRO) instrument. The instrument will transmit data to a technology service provider database, where it will be stored as electronic source for efficacy endpoints. A paper back-up VMS diary card will be used in case of device malfunction, stolen or lost.

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 for the study to ensure data accuracy, completeness and consistency. Any discrepancies found during the eCRF review or during data validation and/or quality assurance 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 a declaration on the eCRF 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 in 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 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.

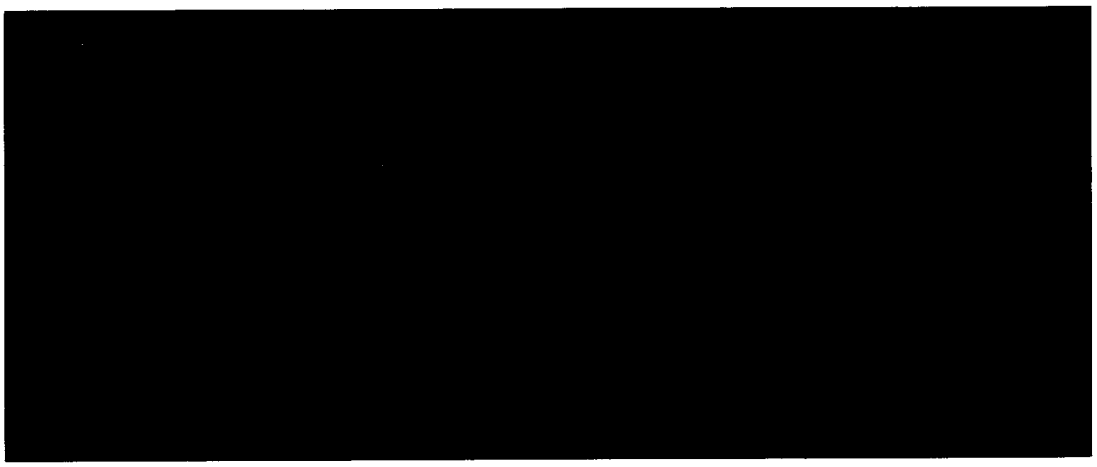
9.3 Data processing

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, including electronic VMS diary data, will be made available for statistical analysis according to the methods outlined in Section 10 and the 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 Organization (WHO) 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



10.2 Analysis sets

Statistical analyses will be based on separate population sets, defined in Table 4.

Table 4 Analysis Populations

Analysis Population	Definition
Randomized population	All subjects randomized
Safety population	All randomized subjects who receives at least 1 dose of study medication
Intent-to-treat (ITT) population	All randomized subjects who have at least 1 post-baseline efficacy assessment
Per-protocol (PP) population	All ITT subjects who do not have any major protocol deviations
PK population	All randomized subjects who received at least 1 dose of MT-8554 and who have at least 1 post-dose value for plasma concentration without important protocol deviations which may affect the PK of MT-8554

Abbreviations: PK=pharmacokinetics

The ITT population will be used for all clinical efficacy analyses. The PP population will also be used for the primary and secondary efficacy endpoints analyses for confirming robustness. The Safety population will be used for all safety summaries. PK assessments will be performed using the PK population.

10.3 Statistical analysis

10.3.1 General considerations

A SAP containing definitions of analysis populations and baseline points, detailed data handling, analysis methods, detailed methods and criteria for the interim analysis, and

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 CSR.

The statistical analysis will be performed using SAS® Version 9.2 or higher. The ITT population will be used for all clinical efficacy analysis; the PP population will also be used for the primary and secondary endpoints for confirming robustness. The Safety population will be used for all safety summaries. PK assessments will be performed using the PK population. All formal statistical tests will be done at the 5% two-sided significance level. Point estimates will have 2-sided 95% confidence intervals (CIs) where applicable.

Where appropriate, variables will be summarized descriptively (frequency and percent will be summarized for categorical variables; mean, standard deviation [SD], median, minimum, and maximum will be presented for continuous variables) by study visit and by treatment group.

All individual subject data will be listed, where applicable.

Baseline for VMS frequency is the sum of the number of moderate and severe VMS recorded in the daily VMS diary between Day -7 and Day -1, divided by the number of days with data. Baseline for VMS severity is the defined value (see below) between Day -7 and Day -1.

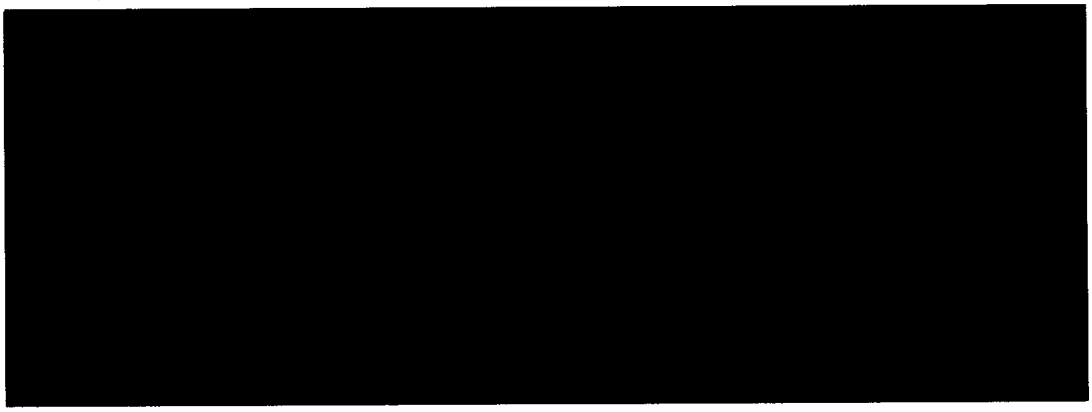
A daily severity score of zero (0) will be assigned if it will be reported that no VMS occurred on that day.

10.3.2 Data handling

There will be no imputation of the missing data for the primary analysis. The details of the missing data handling for sensitivity analysis will be provided in the SAP.

10.3.3 Interim analysis

In addition to on-going safety monitoring, there will be one planned interim assessment for safety and one planned interim analysis for efficacy (futility) and safety.



The interim analysis will be conducted by an independent statistician supporting the DMC, who will evaluate the interim analysis results with unblinded data. The DMC will review the data and provide recommendations to the Sponsor.

10.3.4 Analysis of demography and other baseline subject characteristics

Demographic and other baseline variables include age, sex, height, weight, BMI, ethnic origin, and medical history.

Age, sex, height, weight, BMI, ethnic origin will be summarized. Age will be calculated as the integer difference in years from date of birth to informed consent date. Medical history will be listed by subject.

10.3.5 Analysis of primary endpoints

Main Analysis

Change from baseline to Week 4 and Week 12 in the average daily frequency of moderate to severe VMS will be analyzed using a repeated measures analysis of covariance (ANCOVA) model with an unstructured covariance structure. The analysis model will include baseline value of the endpoint as a covariate; weeks, treatment, antidepressant using (Y,N), and interaction between antidepressant using (Y,N) and treatment as fixed effect. Relevant covariates will also be included in the model. If the normality assumption for the model is not met, a non-parametric method such as a ranked analysis of variance (ANOVA) will be performed.

The sensitivity analysis will be conducted using primary analysis model with applicable covariates for ITT subjects without using antidepressants.

Similar analyses will be conducted for VMS severity.

Comparison between each dose of MT-8554 and placebo will also be conducted using a repeated measures ANCOVA model. Point estimates and 95% CIs for the difference between each active dose and placebo will be obtained.

Further details will be provided in the SAP.

Secondary Analysis

The primary endpoints will also be analyzed using Maximum Contrast Methods with baseline value of the endpoint as a covariate, or slope approach[13], as an analysis of the dose-response relationship. The detail will be specified in the SAP.

The primary endpoints will also be analyzed using an ANCOVA model.

10.3.6 Analysis of secondary endpoints

After the main analyses for all co-primary endpoints successfully show the treatment effect, efficacy analyses for the secondary endpoints may be continued in a fixed order as deemed appropriate as follows.

1. The proportion of responders at Weeks 4 and 12 (i.e., subjects with cutoff number* or greater reduction in the average daily frequency of moderate and severe VMS compared to baseline).
2. Time to response, defined as time (in weeks) from randomization to the first time subjects meet responder criteria (i.e., cutoff number* or greater reduction from baseline in the average daily frequency of moderate and severe VMS).
3. Change from baseline to Weeks 4 and 12 in the ISI total score.

*Note: The cutoff number of responder criteria will be calculated using anchor-based method, using PGIC as the anchor. The satisfied subjects will be defined as those whose PGIC response is either 6 or 7. The cutoff number is defined as numerical value to maximize the sum of sensitivity and specificity for change from baseline in average daily frequency of moderate to severe VMS. This calculation will use weeks4, 12 and 4 arms pooled data.

The proportion of responders will be analyzed using a logistic regression model with treatment as fixed effect and baseline as covariate.

The time to response will be analyzed with a log-rank test for each MT-8554 arm with placebo, with treatment as fixed effect and baseline as covariate. The VMS severity score and ISI will be analyzed using a procedure similar to the main analyses for co-primary endpoints.

Further details will be provided in the SAP.

10.3.7 Analysis of other efficacy endpoints

Summary statistics will be presented for the MENQOL change from baseline to Week 12.

Other efficacy endpoints will be summarized by treatment groups using descriptive statistics. Further details will be provided in the SAP.

10.3.8 Subgroup analysis

The primary analysis model with applicable covariates will be conducted for ITT subjects who used antidepressants during the study. More subgroup analyses may be defined in the SAP.

10.3.9 Safety evaluation

AEs are considered as treatment emergent if they occur after the first dose administration of randomized study medication or if a pre-dose event increases in severity following dosing. The frequency and incidence of treatment emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall. Summary listings will be constructed by relationship to study medication and by maximum severity. Serious TEAEs and TEAEs leading to study medication discontinuation will be provided as listings.

Vital signs, ECG parameters, and clinical laboratory results will be summarized by treatment group and planned sampling point.

Other safety measurements (e.g., endometrial and breast safety evaluations) will be summarized according to the data type.

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

10.3.10 Pharmacokinetic evaluation

All PK data will be listed and summarized using the number of observations, mean, SD, coefficient of variation (CV%), median, minimum, maximum, geometric mean,

and geometric CV%. PK concentrations will be summarized by treatment and planned sampling time.

Population PK analysis will be performed using the plasma concentration of MT-8554 obtained in this study in combination with data obtained from other clinical studies. Population PK analysis results will be reported separately from the CSR. Details of the population PK analysis will be presented in a modelling plan.

10.3.11 Other data evaluation

The prior and concomitant medication, treatment exposure, compliance and other applicable data will be summarized by treatment groups appropriately.

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 Conference on Harmonization 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 IRB/EC approved ICF will be given to each subject.

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

11.2.2 Ethical and regulatory approval

The study will be 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 Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
3. Food and Drug Administration Code of Federal Regulations (21 CFR)

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 IRB, FDA, and local 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 IRB(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 study medication are reported promptly to the regulatory authorities.

If it is necessary to amend the protocol during the study, proper notification will be made to the regulatory authorities and IRBs in the form of a Protocol Modification. Protocol Modification requiring IRB approval may be implemented only after a copy of the IRB's approval/favorable opinion letter has been transmitted to the Sponsor and regulatory authority approval has been obtained (if required). Protocol Modifications that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to receiving Sponsor, FDA and/or IRB 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 FDA and the IRB.

11.2.3 Source document requirements and document access during the study

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation (including, but not limited to: essential documents, copies of protocols, eCRFs, source data such as original reports of test results, study medication 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, IRB 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.

11.2.5 Protocol deviations

The Sponsor does not allow prospective deviations from the protocol. Any significant deviations affecting subject eligibility and/or safety must be reviewed or approved by the IEC/IRB and regulatory authority, as applicable. The Investigator is responsible for complying with all protocol requirements, and applicable to laws pertaining to protocol deviations. If a protocol deviation occurs (or is retrospectively identified) after a subject has been enrolled, the Investigator is responsible for notifying their IEC/IRB, regulatory authorities (as applicable), and assigned Clinical Monitor or Sponsor.

11.3 Data monitoring committee

An independent DMC, composed of experts in the management of subjects with the disease under study will be established for MT-8554-A01 according US FDA guidance. An independent biostatistician will be assigned to the DMC to maintain the integrity of the study blind and provide safety data at regular predefined intervals during the study and provide the interim analysis to the DMC.

[redacted]

A DMC charter will outline the scope and key responsibilities, timing of reviews, communications between the DMC and the Sponsor, and recommendations and action rules for the study.

11.4 Central reading of transvaginal ultrasound

The scans will be performed locally by qualified personnel and blinded review will be conducted centrally. The scan at baseline will also be read locally by the Investigator for the exclusion criterion #8.

11.5 Endometrial biopsy adjudication committee

An endometrial biopsy adjudication committee, composed of three pathologists, will be established for MT-8554-A01. The endometrial tissue obtained by endometrial biopsy will be processed in the same manner by a central laboratory. Three independent expert pathologists, blinded to treatment group and to each other's readings, determine the diagnosis for endometrial biopsy slides during the conduct of the study.

A charter for adjudication committee will outline the scope and key responsibilities, timing of reviews, communications between the adjudication committee, the DMC, the Investigator site and the Sponsor.

11.6 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 11.8.

11.7 Quality assurance and auditing

Authorized representatives of the Sponsor, IRBs, and/or regulatory authorities may conduct an audits or inspections 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.

11.8 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 study medication
- Review of Investigator site study records for completeness

Any unresolved AEs of SAEs will be followed according to Section 8.10.

11.9 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.

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 IRB, 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 5.2.3.2).

Any unresolved AEs or SAEs will be followed up according to Section 8.10.

The Investigator must make every effort to contact the subject to review all AEs. In the event that a subject drops out of the study at any time, the reason for discontinuation 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 11.8.

11.10 Premature discontinuation of individual Investigator sites

The Sponsor may at any time, at its sole discretion, discontinue the Investigator site for various reasons, including, without limitation, the following:

- Failure of the Investigator to enroll subjects into the study at a reasonable rate
- Failure of the Investigator to comply with applicable laws and/or pertinent regulations
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or regulatory authorities
- Insufficient adherence to Protocol requirements

The Sponsor will issue a written notice to the Investigator, which will contain the reasons for taking such action. If the Investigator site is terminated for non-compliance, appropriate regulatory authorities will also be notified by the Sponsor.

For all subjects, the Follow-up visit assessments should be performed, as far as possible (Section 5.2.3.2).

Any unresolved AEs or SAEs will be followed up according to Section 8.10.

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 drops out of the study at any time, the reason for discontinuation must be fully documented in the source documents and the CRF. 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 11.8.

11.11 Liability and insurance

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

12 DISCLOSURE OF DATA

12.1 Confidentiality

All information concerning MT-8554 is the sole property of the Sponsor. For the avoidance of doubt, the Sponsor has full ownership of the eCRFs completed as part of the study. 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.

Subjects will be informed that all personal information made available for inspection will be handled in confidence and in accordance with applicable laws and regulations. All personnel involved in the study will observe and work within the confines of applicable data protection regulations.

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 will retain ownership of all data. All proposed publications based on the study will be subject to the Sponsor's approval requirements.

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.

13 REFERENCES

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