Study Protocol

Protocol Number: MT-8554-A02

An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT-8554-A01

Protocol Version: Final incorporating Amendment 5
Protocol Amendment Date: 13 August 2019

NCT number: NCT03541200

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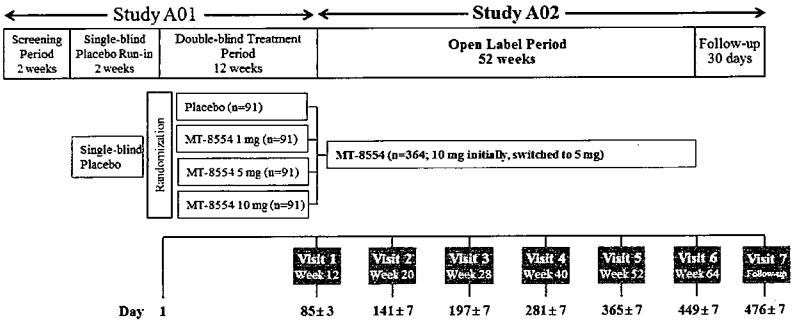
An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT-8554-A01

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
Protocol Date:	13 August 2019

PROTOCOL SYNOPSIS

Protocol number:	MT-8554-A02
Protocol title:	An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT-8554-A01
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:	MT-8554 [redacted] mg capsules
Treatment regimen:	• Dose : MT-8554 5 mg* • Route : Oral • Frequency : Once daily before bedtime *Note: Based upon the results of Study MT-8554-A01, the dose is changed from 10 mg to 5 mg because participating subjects will no longer derive potential clinical benefit from receiving 10 mg dose. All participating subjects who reconsent to continue the study will receive MT-8554 5 mg.
Treatment duration:	Subjects will participate in the open-label period for 52 weeks
Objectives:	**Primary Objective:** To assess long-term safety and tolerability of MT-8554. **Secondary Objectives:** • To assess long-term efficacy of MT-8554 on VMS frequency and severity. • To assess long-term efficacy of MT-8554 on quality of life as measured by Menopause Specific Quality of Life (MENQOL).
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:	It is planned to enroll up to 364 subjects who have completed Study MT-8554-A01. The study will be finished when approximately 100 subjects complete a 52-week open-label treatment period and 30-day follow-up.

Study design:	
Study methodology:	Study MT-8554-A02 is an open-label, long-term safety extension trial of Study MT-8554-A01. The study will be initiated during the conduct of Study MT-8554-A01. Subjects who complete the preceding trial, Study MT-8554-A01, and comply with eligibility criteria for Study MT-8554-A02 will be enrolled in a 52-week open-label treatment period. Visit 7 (Week 12) of Study MT-8554-A01 will be considered Visit 1 of Study MT-8554-A02. Assessments already carried out at Visit 7 (Week 12) of Study MT-8554-A01 will not be repeated. During the 52-week open-label treatment period, subjects will attend visits every 8 weeks between Visits 1 and 3 (Weeks 12, 20, and 28) and every 12 weeks between Visits 4 and 6 (Weeks 28, 40, 52, and 64). All enrolled subjects will receive MT-8554 (was 10 mg initially, switched to 5 mg*) for 52 weeks. Study drug will be administered once daily before bedtime. An End of Study (EOS) Follow-up visit will be conducted by phone for safety follow-up 30 days after the end of the open-label treatment period. *Note: Based upon the results of Study MT-8554-A01, the dose is changed from 10 mg to 5 mg because participating subjects will no longer derive potential clinical benefit from receiving 10 mg dose. All participating subjects who reconsent to continue the study will receive MT-8554 5 mg.
Main inclusion criteria:	1. Signed informed consent to participate in this study. 2. Subjects who complete the preceding trial (Study MT-8554-A01) through Week 12. 3. In the Investigator's opinion, subject is able to understand the nature of the study, any risks involved in participation, and is willing to cooperate and comply with the protocol restrictions and requirements including transvaginal ultrasound and endometrial biopsy.

Main exclusion criteria:	Subjects who meet the withdrawal criteria for the preceding trial (Study MT-8554-A01).
Endpoints:	**Safety Endpoints (Primary objectives)** • Physical examination (including breast safety evaluation). • Vital signs (blood pressure, pulse and tympanic body temperature). • Electrocardiogram (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). • Breast safety (breast tenderness and incidence of breast cancer) • Depression and anxiety as measured by 8-Item Patient Health Questionnaire (PHQ-8) and Generalized Anxiety Disorder-7 (GAD7), respectively. **Exploratory Endpoints** • Frequency of VMS, which is 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. • Severity of VMS, which is 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 open label 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. • MENQOL.
Statistical methods:	<u>Sample size consideration:</u> This study is an open-label extension of Study MT-8554-A01. There is no formal sample size estimation for this study. It is planned to enroll up to 364 subjects from Study MT-8554-A01.

	The subjects who have completed Study MT-8554-A01 and comply with all eligibility criteria may be enrolled into this study. Analysis Populations: • Safety Population includes all subjects who received at least 1 dose of study medication. • Intent-to-treat (ITT) population includes all subjects who have at least 1 post-baseline efficacy assessment. Statistical Methods: Where appropriate, data 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. Safety evaluation: AEs are considered as treatment-emergent if they occurred after administration of the first dose of 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 assessments, and physical examinations will be summarized by treatment group and planned sampling point. Other safety measurements (e.g., endometrial and breast safety measures, reproductive hormones, and depression [PHQ-8 and GAD7] evaluations) will be summarized in tables according to the data type. The graphs will be generated for the endpoints as needed. The data will be presented in data listings as needed. Any other safety data will be presented in tables or listings as appropriate.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
CI	Confidence interval
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical Study Report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
E2	Estradiol
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GAD7	7-Item Generalized Anxiety Disorder questionnaire
GCP	Good Clinical Practice
HDPE	High density polyethylene
hTRPM	Human transient receptor potential melastatin 8
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause Specific Quality of Life
MTDA	Mitsubishi Tanabe Pharma Development America, Inc.
NCS	Not clinically significant
NOAEL	No observed adverse effect level
OLE	Open-label extension
PHQ-8	8-Item Patient Health Questionnaire
PK	Pharmacokinetic(s)
PP	Per-Protocol
PRO	Patient-reported outcome
PT	Preferred term
QTc	Corrected QT interval
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse event
TEAE	Treatment-emergent adverse event
TRPM8	Transient receptor potential melastatin 8
VMS	Vasomotor symptoms

Abbreviation	Definition
WHO	World Health Organization
WMA	World Medical Association

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CONTACT LIST

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[redacted] Vice President and Head, Clinical Development	Sponsor's Responsible Signatory
[redacted] Early Development Team Leader for MT-8554, Clinical Development	Sponsor's Responsible Physician

SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MT-8554-A02

An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT-8554-A01

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).

Vice President and Head, Clinical Development

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

SIGNATURE PAGE (SPONSOR'S RESPONSIBLE SIGNATORY)

Protocol Number: MT-8554-A02

An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT-8554-A01

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[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

SIGNATURE PAGE (STATISTICIAN)

Protocol Number: MT-8554-A02

An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT 8554-A01

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

[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-A02

An open-label, long-term extension study of MT-8554 in postmenopausal women experiencing moderate to severe vasomotor symptoms who completed Study MT-8554-A01

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 the transient receptor potential cation channel family 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 postmenopausal 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.

After menopause, up to 85% of American women have VMS, and many are affected by insomnia and sleep disturbances. Although most symptoms resolve spontaneously after about 5 years, symptoms continue in a substantial number of women[4,5]. Hence, this study will also assess the long-term safety of MT-8554 according to the International Conference on Harmonization (ICH)-E1 guideline.

1.1 Non-clinical pharmacology

[redacted]

1.2 Non-clinical safety pharmacology

[redacted]

[redacted]

1.3 Non-clinical toxicology

General toxicity of MT-8554 was assessed in rats and monkeys. The approximate lethal

[redacted]

1.4 Clinical studies

[redacted]

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

2.1.1 Primary objective

To assess long-term safety and tolerability of MT-8554.

2.1.2 Secondary objectives

- To assess long-term efficacy of MT-8554 on VMS frequency and severity.
- To assess long-term efficacy of MT-8554 on quality of life as measured by Menopause Specific Quality of Life (MENQOL).

2.2 Study endpoints

2.2.1 Safety endpoints (Primary objective)

- Physical examination (including breast safety evaluation).
- Vital signs (blood pressure, pulse and tympanic body temperature).
- Electrocardiogram (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).
- Breast safety (breast tenderness and incidence of breast cancer).
- Depression and anxiety as measured by 8-Item Patient Health Questionnaire (PHQ-8) and by Generalized Anxiety Disorder-7 (GAD7), respectively.

2.2.2 Exploratory Endpoints

- Frequency of VMS, which is 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.
- Severity of VMS, which is 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 open label 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.
- MENQOL.

3 STUDY DESIGN

3.1 Overall study design

Study MT-8554-A02 is an open-label, long-term safety extension trial of Study MT-8554-01. The study will be initiated during the conduct of Study MT-8554-A01.

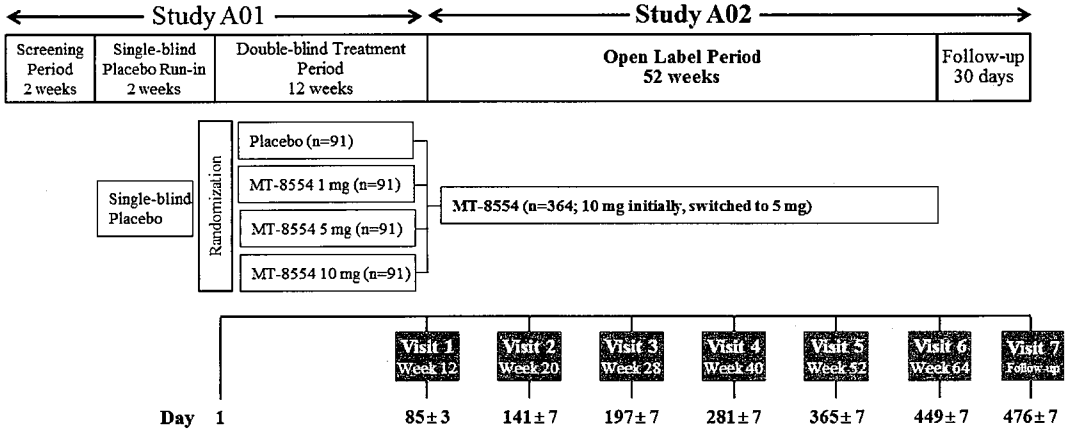
Subjects who complete the preceding trial (Study MT-8554-A01) and comply with eligibility criteria for Study MT-8554-A02 will be enrolled in a 52-week open-label treatment period. Visit 7 (Week 12) of Study MT-8554-A01 will be considered Visit 1 of Study MT-8554-A02. Assessments already carried out at Visit 7 (Week 12) of Study MT-8554-A01 will not be repeated. During the 52-week open-label treatment period, subjects will attend visits every 8 weeks between Visits 1 and 3 (Weeks 12, 20, and 28) and every 12 weeks between Visits 3 and 6 (Weeks 28, 40, 52, and 64).

All enrolled subjects will receive MT-8554 (was 10 mg initially, switched to 5 mg*) for 52 weeks. Study drug will be administered once daily before bedtime.

An End of Study (EOS) Follow-up visit will be conducted by phone for safety follow-up 30 days after the end of the open-label treatment period (see Figure 1).

*Note: Based upon the results of Study MT-8554-A01, the dose is changed from 10 mg to 5 mg because participating subjects will no longer derive potential clinical benefit from receiving 10 mg dose. All participating subjects who reconsent to continue the study will receive MT-8554 5 mg.

Figure 1 Study Design Schematic



3.2 Rationale for study design and treatment regimens

The objectives of this study are to obtain long term safety and tolerability data for MT-8554 when administered once daily before bed time in postmenopausal women with moderate to severe VMS who completed Study MT-8554-A01 according to the ICH-E1 guideline.

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 assess long-term safety and tolerability of MT-8554.

[redacted]

In the preceding study (Study MT-8554-A01), 5 mg was chosen as the medium dose, 1 mg was selected as a low dose to seek a minimal efficacious dose, and 10 mg/day as a high dose to seek a maximum efficacious dose.

All subjects entering in the study were initially allocated to 10 mg of MT-8554 for a further 52 weeks.

Based upon the results of Study MT-8554-A01 (Section 1.4), the dose is changed from 10 mg to 5 mg because participating subjects will no longer derive potential clinical benefit from receiving 10 mg dose. All participating subjects who reconsent to continue the study will receive MT-8554 5 mg.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

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

4.1 Number of subjects

It is planned to enroll up to 364 subjects who have completed Study MT-8554-A01. The study will be finished when approximately 100 subjects complete a 52-week open-label treatment period and 30-day follow-up.

4.2 Recruitment methods

This study will enroll subjects who complete Study MT-8554-A01 and comply with eligibility criteria.

4.3 Inclusion criteria

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

1. Signed informed consent to participate in this study.
2. Subjects who complete Study MT-8554-A01 through Week 12.
3. In the Investigator's opinion, subject is able to understand the nature of the study, any risks involved in participation, and is willing to cooperate and comply with the protocol restrictions and requirements including transvaginal ultrasound and endometrial biopsy.

4.4 Exclusion criteria

A subject will NOT be eligible for this study if the subject meets the withdrawal criteria for Study MT-8554-A01.

4.5 Withdrawal of individual subjects

4.5.1 Discontinuation from treatment

Investigators may choose to temporarily or permanently discontinue study treatment for any reason, including AEs or tolerability.

[redacted]

If any clinically significant abnormality is detected on the clinical breast exam (see Section 6.5.2) at baseline or anytime during the study or there is any occurrence of unexplained uterine bleeding, study medication should be discontinued and subject should be referred to the specialists for further investigations per current standards. If all the required investigations such as physical examination of the breast, imaging and pathology are negative and available within 6 weeks, subject can resume study medication.

An unscheduled study visit can be used to reassess subject's symptoms and willingness to resume study drug.

If treatment is discontinued and the subject 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 declining to continue 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 8.8 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 withdraw from the study
- The subject is lost to follow-up
- The subject is diagnosed with breast cancer
- The subject 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 endometrial thickness of ≥5 mm as measured by transvaginal ultrasound at Week 12, assessed centrally (subject with insufficient imaging data will have repeat transvaginal ultrasound)
- The subject has an abnormal endometrial biopsy result at Week 12, as assessed by the endometrial biopsy adjudication committee.
- 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.)
- 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)
- 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 end of treatment (EOT) visit assessments should be performed, as far as possible (Sections 5.2.1.3 and 5.2.2) 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 discontinues from the study at any given time, the reason for discontinuation must be fully documented in the source documents and the eCRF. The Investigator and or 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.

4.6 Study completion criteria

The study will be completed by the Sponsor when approximately 100 subjects complete a 52-week open-label treatment period and 30-day follow-up. Further treatment of study drug will not be allowed. At the completion of the study all subjects will be required to have EOT visit assessments within the defined visit window. All subjects will be followed for 30 days for AEs, and unresolved AEs or SAEs will be followed up according to Section 8.10.

4.7 Study 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.

4.8 Lifestyle restrictions

Subjects must adhere to the following restrictions:

4.8.1 Alcohol restrictions

Subjects are prohibited from excessive consumption of drink and of food containing alcohol (>2 units* per day) at all times from Visit 1 through the Follow-up visit.

*Note: 1 unit of alcohol is equivalent to 8 g of pure alcohol.

4.8.2 Caffeine and xanthines

Subjects should avoid excessive consumption or an increase in consumption from Visit 1 of food or drink containing caffeine and methylxanthine (e.g., coffee, tea, cola, energy drinks, or chocolates) at all times from Visit 1 through the Follow-up visit. (Increased xanthines intake can interfere with assessment of sleep quality)

4.8.3 Contraception

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

4.8.4 Diet

Subjects will be required to fast (except for water) for 6 hours after dosing at the night prior to Visit 1.

5 STUDY PLAN

Study assessments are summarised in the Time and events schedule (Table 1).

Table 1 Schedule of Assessments

Study Period	Open-label extension						Follow-up
Visit Number	Visit 1[1]	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6 (EOT)	Visit 7 (EOS)
Study Week[2]	Week 12[3]	Week 20	Week 28	Week 40	Week 52	Week 64[4]	Week 68[5]
Study Day ±Window[2]	Day 85 ±3	Day 141 ±7	Day 197 ±7	Day 281 ±7	Day 365 ±7	Day 448 ±7	Day 476 ±7
Informed consent	X						
Inclusion/exclusion criteria	X						
Physical examination[6]	X	X	X	X	X	X	
Breast examination	X					X	
Body weight	X			X		X	
Vital signs[7]	X	X	X	X	X	X	
12-lead ECG	X			X		X	
Routine lab tests	X	X	X	X	X	X	
Transvaginal ultrasound[8]	X					X	
Endometrial biopsy[8]	X					X	
Reproductive hormones[9]	X					X	
PHQ-8 and GAD7	X		X			X	
VMS diary	←	———	———	———	———	→	
MENQOL	X		X			X	
Dispensing MT-8554[10]	X	X	X	X	X		
Drug accountability	X	X	X	X	X	X	
Adverse events	←	———	———	———	———	———	→
Concomitant medication	←	———	———	———	———	———	→
Compliance [redacted] Calls to Subjects[11]	←	———	———	———	→		

Abbreviations: ECG=Electrocardiogram; EOS=End of Study; EOT=End of Treatment Visit; GAD7=Generalized Anxiety Disorder-7 Questionnaire; MENQOL=Menopause Specific Quality of Life; PHQ-8=Eight-Item Patient Health Questionnaire; VMS=vasomotor symptoms.

1. Visit 7 (Week 12) of Study MT-8554-A01 will be considered Visit 1 of Study MT-8554-A02.
2. Study weeks and study days are in reference to the randomization performed on Day 1 in Study MT-8554-A01.
3. Assessments already carried out at Week 12 of Study MT-8554-A01 will not be repeated.
4. The EOT should be performed for subjects who complete treatment as well as those who withdraw from the study early.
5. The Follow-up visit, EOS, 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.
6. Physical examination (abdominal, cardiovascular, general appearance, respiratory, and other) will be performed..
7. Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature) will be measured at all visits.

8. Transvaginal ultrasound and endometrial biopsy to be performed only on subjects who have a uterus. Pelvic examination will be performed only with endometrial biopsy.
9. Luteinizing hormone (LH), follicle stimulating hormone (FSH) and estradiol (E2) will be measured.
10. Subjects will receive 5 mg* of MT-8554 once daily. Investigators should instruct subjects to administer dose at least 2 hours after starting the evening meal and approximately 30 minutes before bedtime.
    *Note: Based upon the results of Study MT-8554-A01, the dose is changed from 10 mg to 5 mg because participating subjects will no longer derive potential clinical benefit from receiving 10 mg dose. All participating subjects who reconsent to continue the study will receive MT-8554 5 mg.
11. Site staff will make periodic calls to the subjects at a minimum of every 4 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 informed consent form (ICF), as described in Section 11.2.1.

Based upon the results of Study MT-8554-A01, the dose is changed from 10 mg to 5 mg. The Investigator (or designated personnel) will ensure that the participating subject must provide reconsent to continue the study and the subject who reconsent to continue the study will receive MT-8554 5 mg.

5.2 Description of study phases

5.2.1 Open-label extension

5.2.1.1 Visit 1: Treatment period (Week 12)

Subjects who have completed Study MT-8554-A01 and comply with eligibility criteria will be enrolled in this study. Subjects will be requested to attend the clinic after a 6-hour fasting period (except for water).

Signed informed consent will be obtained before any procedures are performed. The following assessments will be performed. (Assessments already carried out at Week 12 of Study MT-8554-A01 will not be repeated; refer to Table 1 for further details):

- Signed informed consent
- Inclusion/exclusion criteria
- Physical examination (see Section 6.5.1)
- Breast examination
- Body weight
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- 12-lead ECG
- 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)
- PHQ-8 and GAD7
- MENQOL assessment

- Dispensing MT-8554
- Drug Accountability for Study MT-8554-A01
- AE and concomitant medication recording.
- Diary compliance [redacted] reminder

5.2.1.2 Visits 2 to 5 (Treatment period, Weeks 20, 28, 40, and 52)

Subjects will attend visits every 8 weeks between Visits 1 and 3 (Weeks 12, 20, and 28) and every 12 weeks between Visits 3 and 6 (Weeks 28, 40, 52, and 64). The following assessments will be performed (refer to Table 1 for further details):

- Physical examination (see Section 6.5.1)
- Body weight (Visit 4 only)
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- 12-lead ECG (Visit 4 only)
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- PHQ-8 and GAD7 (Visit 3 only)
- MENQOL (Visit 3 only)
- Review VMS diary (re-educate subject if necessary)
- Dispensing MT-8554 (Visits 2 to 5 only)
- Drug Accountability
- AE and concomitant medication recording.
- Diary compliance [redacted] reminder

5.2.1.3 Visit 6: EOT (Week 64 or early termination)

Subjects will attend the last visit of the treatment period and the following assessments will be performed (refer to Table 1 for further details):

- Physical examination (see Section 6.5.1)
- Breast examination
- Body weight
- Vital signs (including sitting blood pressure, pulse rate, and tympanic body temperature)
- 12-lead ECG
- Routine laboratory evaluations (hematology, biochemistry, coagulation, and urinalysis)
- Transvaginal ultrasound and Endometrial biopsy (for subjects with a uterus)
- Reproductive hormone assessments: E2, LH, and FSH
- PHQ-8 and GAD7
- MENQOL
- VMS diary collection
- Drug Accountability
- AE and concomitant medication recording.

5.2.2 Follow-up

5.2.2.1 Visit 7: Follow-up Visit (FU, Week 68 or 4 weeks after early termination)

Subjects who complete the study (or subjects who withdraw from treatment early) 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.

5.2.3 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.

5.2.4 Phone Calls to Subject

Sites will make periodic calls to subjects at a minimum of every 4 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.

5.2.5 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 Institutional Review Board (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 subject characteristics (date of birth, sex, weight, height, and race) have been recorded at Screening in Study MT-8554-A01.

6.3 Medical history

The medical, drug, smoking, alcohol, and surgical history have been recorded at Screening in Study MT-8554-A01. Medical/surgical history includes any medical condition or surgical history prior to Screening.

6.4 Concomitant medication

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 Visit 1 through the final Follow-up assessment.

[redacted]

[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 are 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 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 Safety assessments

Please refer to Section 8 for details of AE management.

6.5.1 Physical examination

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

6.5.2 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 Week 12 and Week 64 or early termination. The Investigator or designated study staff will perform a clinical examination and record in the eCRF.

If the breast examination is found to be 'abnormal clinically significant', the subject is instructed to discontinue the study drug and proceed with follow-up management per standards of care including mammogram, ultrasound and biopsy. If breast lesion is considered benign after complete evaluation of subject and investigations, subject will be allowed to resume the study medications within 6 weeks of interruption of study medication.

6.5.3 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 for safety purposes and the recording will be reported as 'normal', 'abnormal clinically significant (CS)', or 'abnormal not clinically significant (NCS)'.

Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

6.5.4 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 for safety purposes and the recording will be reported as 'normal', 'abnormal CS', or 'abnormal NCS'. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed if needed.

6.5.5 Transvaginal ultrasound

For subjects who have a uterus, a transvaginal ultrasound will be performed at Week 12 and Week 64 or early termination to measure endometrial thickness. The scans will be performed locally by qualified personnel and blinded review will be conducted centrally. Procedures for the handling of these assessments will be described in full in separate documents.

6.5.6 Endometrial biopsy

For subjects who have a uterus, an endometrial biopsy will be performed at Week 12 and Week 64 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 Visits 1 and 6.

6.5.7 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 2.

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 2 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. Visit 3 and Visit 6 (end of treatment [EOT], Week 64, or early termination) only.
2. Performed only if required, based on urinalysis results.

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

6.6 Safety-related questionnaires

6.6.1 Eight-Item Patient Health Questionnaire[6]

The PHQ-8 is a self-rated questionnaire assessing current depressive symptoms based on 8 out of 9 criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). See APPENDIX 1 for an example of the PHQ-8.

6.6.2 Generalized Anxiety Disorder-7[7]

The GAD7 is a self-rated questionnaire assessing current anxiety levels. See APPENDIX 2 for an example of the GAD7.

6.7 Efficacy assessments

6.7.1 Subjective vasomotor symptoms

Subjects will be asked to record frequency and severity of VMS in an electronic diary beginning at Visit 1 and throughout the open label treatment period. See APPENDIX 3 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. 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 3.

Table 3 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

6.7.2 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 4 for an example of the MENQOL.

7 STUDY MEDICATIONS, TREATMENT AND DOSING REGIMEN

7.1 Investigational Medicinal Product

7.1.1 Drug product

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

Bulk capsules will be packed in [redacted] Individual subject doses will be packed in [redacted]

MT-8554 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 Compliance 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) 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 Visit 6 (EOT, Week 64, or early termination).

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

Capsules will be provided in [redacted] mg capsules. Study drug will be provided to the study sites [redacted] and should be stored according to the study medication clinical label.

MT-8554 capsules must be dispensed in [redacted]. Subjects will be instructed to store the medication per the study medication 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 study medication 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 excursions 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 bottles 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 site 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 at least 2 hours after starting their evening meal and approximately 30 minutes before bedtime.

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

7.2.1 Compliance

The prescribed dosage, timing and mode of administration of study medication may not be changed. Any departures from the intended dose regimen must be recorded in the eCRF.

Study medication accountability and subject compliance will be documented throughout the OLE period using study medication dispensing and return record logs.

Subjects will be asked to return all unused medication including empty and partially used bottles. Study medication dispensed at the previous visit will be collected by the site and compliance will be assessed by counting the returned drug.

Non-compliance is defined as taking [redacted] of study medication during any visit.

7.3 Subject identification

Each subject will be identified by the unique Subject Number that was assigned to them at the Screening visit of Study MT-8554-A01.

7.4 Procedures for assigning subjects to treatment groups

In this open-label extension study, all subjects who completed Study MT-8554-A01 and who meet criteria for enrolment in Study MT-8554-A02 will receive MT-8554 (was 10 mg initially, switched to 5 mg) for 52 weeks. Study drug will be administered once daily before bedtime (Section 3.1).

Based upon the results of Study MT-8554-A01, the dose is changed from 10 mg to 5 mg. All participating subjects who reconsent to continue the study will receive MT-8554 5 mg. An unscheduled visit will be used to accommodate such change in study drug dose.

8 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs that occur from the time the informed consent is signed 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 'treatment-emergent' if they arise following the first administration of study medication in the OLE period or if an AE which is continued from the preceding trial (Study MT-8554-A01) increases in severity following the first administration of study medication in the OLE period.

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

Medical and scientific 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.4 Relationship of adverse events to Investigational Medicinal Product

The causal relationship of the AE to 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 values are clinically significant. Laboratory abnormalities which are judged by the Investigator to be clinically significant will be recorded as AEs.

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

All clinically significant abnormal laboratory results or assessments will be followed until they resolve (return to normal or baseline values) or 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 on an AE form in the eCRF. Reports should contain a description of the event, date and time of onset, date and time of resolution, severity, treatment required, relationship to 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 are 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 designee immediately.

8.7 Recording and reporting of serious adverse events

All SAEs occurring from the time the informed consent is signed from the 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 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 not 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) and will provide all SAEs to the regulatory authorities and Investigator. 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 and Week 64 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 subjects with AEs/SAEs, until the event has resolved or stabilized and any abnormal laboratory values have returned to baseline; or until there is a satisfactory explanation for the changes observed. In the case of death, if possible a pathologist's full 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 eCRFs and will be substantiated by source documents (such as laboratory reports, medical records or ECGs) at the Investigator site. All relevant data will be transcribed into the eCRF from source documents, entered into the study database directly from source documents, or transferred electronically to the study database. Where no printed or electronic source documents exist, data will be entered directly into the eCRF and the eCRF will be considered the source document.

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 will be made available for statistical analysis according to the methods outlined in Section 10 and the Statistical Analysis Plan (SAP).

AEs and medical history entries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using the World Health 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 and randomization

There is no formal estimation of sample size for inclusion of subjects in Study MT-8554-A02. It is planned to enroll up to 364 subjects who have completed Study MT-8554-A01 and who comply with all eligibility criteria for Study MT-8554-A02.

Study MT-8554-A02 is an open-label extension study of Study MT-8554-A01. All subjects will receive MT-8554 (was 10 mg initially, switched to 5 mg) for 52 weeks. Subjects will not be randomized.

10.2 Analysis sets

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

Table 4 Analysis populations

Analysis Population	Definition
Safety population	All subjects who receives at least 1 dose of study medication
Intent-to-treat (ITT) population	All subjects who have at least 1 post-baseline efficacy assessment

The Safety population will be used for all analyses and summaries. The ITT population will be used for all clinical efficacy analyses.

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 Safety population will be used for all analyses and summaries. Point estimates will have 2-sided 95% CIs where applicable.

Where appropriate, data will be summarized descriptively (frequency and percent will be summarized for categorical variables; mean, standard deviation, 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. The baseline value of Study MT-8554-A02 is the last valid values prior the first dose of Study MT-8554-A02. The baseline value of Study MT-8554-A01 and Study MT-8554-A02 will be used as appropriate.

The Study MT-8554-A01 data are combined with Study MT-8554-A02 data for summary tables and graphs as needed.

10.3.2 Data handling

Procedures for the handling of any missing, unused, or spurious data will be described in the SAP. Data issues found after database lock will be described in the Clinical Study Report (CSR).

10.3.3 Analysis of demography and other baseline subject characteristics

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

Age, sex, height, weight, 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 summarized in table or listed by subject.

10.3.4 Safety evaluation

The safety analysis is the long-term safety and tolerability of MT-8554 during the OLE period.

The safety endpoints vital signs, ECG parameters, clinical laboratory assessments, physical examinations, AEs, endometrial and breast safety measures, reproductive hormones, and depression [PHQ-8 and GAD7] will be summarized in tables according to the data type. The graphs will be generated for the endpoints as needed. The data will be presented in data listings as needed.

Any other safety data and concomitant medication will be presented in tables or listings as appropriate.

Further details will be provided in the SAP.

10.3.4.1 Adverse events

AEs are considered as treatment emergent if they occur after the first dose administration of study medication of Study MT-8554-A02 or if a pre-dose event increases in severity following dosing. The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT), by treatment group and overall. TEAEs will be summarized by treatment, by relationship to study medication and by maximum severity as well. Serious TEAEs and TEAEs leading to study medication discontinuation will be summarized in tables. All AE will be presented in a data listing.

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

10.3.5 Analysis of efficacy endpoints

The efficacy endpoints include Frequency of VMS, Severity of VMS, and MENQOL.

Frequency of VMS is 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. Severity of VMS is 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 open label 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.

All efficacy endpoints and change from baseline of these will be summarized in tables according to the data type. The graphs will be generated for the endpoints as needed. The data will be presented in data listings as needed.

Further details will be provided in the SAP.

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

1. Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
2. ICH Harmonised Tripartite Guidelines for Good Clinical Practice 1996.
3. 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 Independent Ethics Committee (IEC), regulatory 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 IEC(s) in accordance with institutional/local regulations, for example:

- Information on SUSARs
- Periodic reports on the progress of the study

- Notification of the EOS 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 signed 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 Central reading of transvaginal ultrasound

The scans will be performed locally by qualified personnel and blinded review will be conducted centrally.

11.4 Endometrial biopsy adjudication committee

An endometrial biopsy adjudication committee, composed of three pathologists, will be established for MT-8554-A02. 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 Investigator site and the Sponsor.

11.5 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 11.7.

11.6 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.

11.7 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.

11.8 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 5.2.2).

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 EOS 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 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.

In addition, all general Investigator site activities required for the scheduled EOS and site closure should be completed, as described in Section 11.7.

11.9 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 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 5.2.2).

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 EOS 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 EOS assessments.

In addition, all general Investigator site activities required for the scheduled EOS and site closure should be completed, as described in Section 11.7.

11.10 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 the strictest 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

1. Maier C, Baron R, Tölle TR, Binder A, Birbaumer N, Birklein F et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. Pain. 2010;150:439-50.
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3. Freedman RR. Pathophysiology and treatment of menopausal hot flashes. Semin Reprod Med. 2005;23:117-25.
4. Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of menopause. Endocr Pract. 2011;17:1-25.
5. National Institutes of Health State-of-the-Science Panel. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. Ann Intern Med. 2005;142:1003-13.
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7. Kroenke K, Lowe B, Spitzer RL, Williams, JB. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med. 2006;166(10):1092-1097.