Statistical Analysis Plan

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

Version: Final 1.0
Date: 16 Dec 2019

NCT number: NCT03541200

Statistical Analysis Plan

Protocol 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

PREPARED BY:

NAME: [redacted]
POSITION: **Statistician**
VERSION: **Version 1.0**
DATE: [redacted]

APPROVAL FORM

STATISTICAL ANALYSIS PLAN

Protocol No. **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**

Version Version 1.0

Date [redacted]

Authors:

Statistics Author	
Print Name:	[redacted]
Position:	COT STAT

Approved by:

Statistic Approver	
Print Name:	[redacted]
Position:	Responsible STAT
Signature:	[redacted]
Approval date:	

TABLE OF CONTENTS

[redacted]

TABLE OF TABLES

TABLE OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BDRM	Blind data review meeting
BLQ	Below the limit of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically significant
CSR	Clinical study report
DMC	Data Monitoring Committee
DP	Decimal places
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
GCP	Good Clinical Practice
IAO	International Agreed Order
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviation	Definition
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IMP	Investigational medicinal product
IND	Investigational New Drug Application
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
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.
MTPC	Mitsubishi Tanabe Pharma Corporation, Inc.
NCS	Not clinically significant
PHQ-8	8-Item Patient Health Questionnaire
PT	Preferred term
QC	Quality control
QOL	Quality of life
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia's formula
RBC	Red blood cells
SAE	Serious adverse event
SAF	safety population
SAP	Statistical Analysis Plan
SD	Standard deviation

Abbreviation	Definition
SNRI	Serotonin-norepinephrine reuptake inhibitors
SOC	System Organ Class
SSRI	Serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse event
TEAE	Treatment-emergent adverse event
THC	Tetrahydrocannabinol
ULN	Upper limit of normal
US	United States
VMS	Vasomotor symptoms
WBC	White blood cells
WHO	World Health Organization
WMA	World Medical Association

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the MT-8554-A02 final protocol and amendment 4 dated 07 August 2019. The plan covers statistical analysis, tabulations and listings of efficacy, safety data to assess the efficacy and safety of MT-8554(10 mg initially, switched to 5 mg).

The SAP is prepared by MTDA data science and reviewed by MTDA clinical study team and MTPC data science. The statistical analyses and production of the outputs described in the SAP will be conducted and QCed by [redacted] using SAS version 9.4 or higher. The final analyses and outputs will be approved by MTPC/MTDA data science.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1 Study 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).

2.2 Study Endpoints

2.2.1 Safety Endpoints (Primary Endpoints)

- 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 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 Study Design

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.

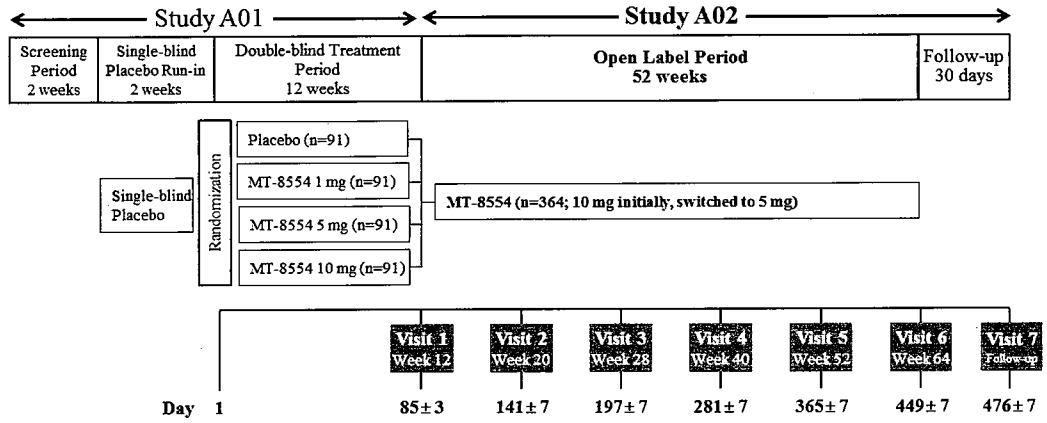
Subjects who complete the preceding trial (Study MT-8554-A01) and comply with eligibility criteria for Study MT-8554-A02 will be enrolled in a 52-week open-label treatment period. Visit 7 (Week 12) of Study MT-8554-A01 will be considered Visit 1 of Study MT-8554-A02. Assessments already carried out at 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 3 and 6 (Weeks 28, 40, 52, and 64).

All enrolled subjects will receive MT-8554 (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.

Figure 1 Study Design Schematic



3.2 Schedule of Study Procedures

Study assessments are summarized 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] requirements.

3.3 Sample Size and Power Considerations

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 enrol 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.

4. PLANNED ANALYSES

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

There is no plan for analyses other than final data analysis .

5. ANALYSIS POPULATION(S)

Statistical analyses will be based on separate population sets, defined in Table 2.

Table 2 Analysis populations

Analysis Population	Definition
Safety(SAF) 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 exploratory assessment

6. GENERAL CONSIDERATIONS

6.1 Descriptive Statistics

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

7. DATA CONVENTION

7.1 Data Handling Convention for Dropouts or Missing Data

For each summaries, only observed data will be used. Unless otherwise specified missing data will not be imputed. Unless otherwise specified, summary statistics will be calculated as long as one non-missing value exists.

For AE start and/or end date missing or partial missing, the AE will be treated as TEAE if it cannot be determined a non-TEAE. If severity or relationship is found to be missing the most severe occurrence will be imputed for the particular summary.

7.2 Analysis Visit Window

The derived analysis visit windows are outlined in Table below.

Table 3 Derived Analysis Visit Windows

Visit		Nominal day	Window
1	Week 12 (Baseline)	NA	NA
2	Week 20	Day 141	Day 113 to 169
3	Week 28	Day 197	Day 170 to 239
4	Week 40	Day 281	Day 240 to 323
5	Week 52	Day 365	Day 324 to 407
6	Week 64	Day 448	Day 408 to 462
7	Week 68 (FU)	Day 476	NA

The analysis visits are derived according to the following criteria:

- The unscheduled visits are not used for the deriving.
- If a study visit is the only one in an analysis window, this study visit becomes the derived analysis visit.
- If there are multiple visits in a visit window, the closest visit to the nominal day becomes the analysis visit. In the event that two visits are the closest visits to the nominal day and equally distanced to the nominal day, the visit after the nominal day becomes the derived visit.
- Unless otherwise specified, the baseline values are the last available assessment before the first dose of study A02.
- The follow-up visit will not be derived. The study visit will be used.
- Unscheduled visits and retests (same visit number assigned), will not be displayed in by-visit summary tables, but will be included in the data listings. All data will be listed. Listings will include treatment, scheduled, unscheduled, retest and early discontinuation data.
- The efficacy endpoints based on diary data use different windows. See Section7.3.3.1.

7.3 Definition of Analysis Variables

7.3.1 Study Subjects

7.3.1.1 BMI

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

It will be rounded off the second decimal place and reported the value to the first decimal place.

7.3.1.2 Medical history

All medical and surgical history will be coded from the actual term using the MedDRA version 20.1.

Medical and surgical history data collected in study A01 will be used.

7.3.1.3 Concomitant medications

Concomitant medication is defined as any medication, other than study medication, which is taken on or after the start day of study A02 treatment.

All concomitant medications will be coded using the WHO drug dictionary (WHO Herbal Dictionary) (Version SEP 2017).

7.3.1.4 Duration of exposure and Cumulative Dosing Count

The duration of exposure is calculated as the total number of days that the subject has been treated with study A02 medication—that is, from the study A02 treatment start date to the date of their EOT/withdrawal visit. For subjects lost to follow up, the treatment end date is taken to be the date of their last visit. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.

Duration of exposure (days) = date of end of treatment visit – date of first dose of study A02 medication; Cumulative Dosing days= Duration of exposure – number of days subject miss the medication.

7.3.1.5 Treatment Compliance

Compliance with study medication—based on the drug accountability data—will be calculated as the number of days subjects take study medication divided by the duration of exposure in days, expressed as a percentage.

Study medication compliance will be calculated as follows:

$$\frac{\text{Cumulative Dosing days}}{(\text{date of end of treatment visit} - \text{date of first dose in A02})} \times 100\%$$

The subjects should take one dose daily per protocol.

7.3.2 Safety Assessments

7.3.2.1 Adverse events (AEs)

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.

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 20.1.

Treatment-emergent AEs (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study medication. The treatment relationship with the AE is in 2 categories (reasonable possibility, no reasonable possibility). The detail is included in protocol.

7.3.2.2 Adverse Reactions

Adverse reactions are defined as adverse events that are determined to have a "reasonably possible" causal relationship to the study drug.

7.3.2.3 Duration of the AE and Time to the AE

Duration of the AE and time to the AE occurrence from start of study A02 medication will be calculated and presented in days, where AE duration = AE stop date – AE start date + 1 and the time to the AE occurrence = AE start date – first study A02 dose date + 1.

7.3.2.4 The Estimated Glomerular Filtration Rate (eGFR)[5]

$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if Black]

S_{Cr} (standardized serum creatinine) = mg/dL

$\kappa = 0.7$ (females) or 0.9 (males)

$\alpha = -0.329$ (females) or -0.411 (males)

min = indicates the minimum of S_{Cr}/κ or 1

max = indicates the maximum of S_{Cr}/κ or 1

Age = years

It will be rounded off the second decimal place and reported the value to the first decimal place.

7.3.2.5 Lab values Below/Above the Limit of Quantitation Deriving

The lab values below the limit of quantification (BLQ) are collected in the form like "< 2" in the clinical data base. In this case the numeric value of the lab is missing value. The cut-off value '2' will be used to impute the missing value for this case. Similarly, for the lab values above the limit of quantification, the cut-off value will be used for the numeric value of the lab.

Table 4 Imputation of lab values below/above the limit of quantification

Lab Test	Characteristic value	Derived Numeric value
Bilirubin	<2	2
Direct Bilirubin	<2	2
Estradiol	<61	61
Luteinizing Hormone	<0.1	0.1
Specific Gravity	>1.045	1.045

7.3.3 Exploratory Assessments

The subjects' diary data will be used to derive the efficacy endpoints. Subjects can use paper diary as contingent back up when they have problem with their ediary device. The paper diary data will be used only for the days that subjects have paper diary without ediary data. This means the paper diary data is not used when ediary data is available.

7.3.3.1 Average daily frequency of moderate to severe VMS

The average daily frequency of moderate to severe VMS at a time point (Week 12, 13, 14, ..., 64) is the average of the frequency of moderate to severe VMS of available diary days in a 7-day window. It will be rounded off the second decimal place and reported the value to the first decimal place. The nominal day for each time point relative to the first dose day will be used. The analysis windows are defined in the table below. The other efficacy endpoints based on average daily VMS diary data will be derived using these windows accordingly.

Table 5Analysis visit windows of diary days used for average daily frequency of moderate to severe VMS

	Nominal day	Window
Week 12 (Baseline)	85	Day 79 to 85
Week k	K*7 + 1	Day K*7 – 5 to K*7 + 1

where k = 13, 14, ..., 64.

VMS data on the day of Week 64 visit is not used for the calculation of average daily VMS frequency.

If the count of available VMS data in a specific week is less than four (4), the latest diaries in the previous window can be carried as needed to make 4 diaries available in this window. Then the average daily VMS frequency in the week is calculated.

7.3.3.2 Average daily severity score of mild to severe VMS

The daily VMS severity score 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. It will be rounded off the third decimal place and reported the value to the second decimal place.

The avarage daily VMS severity of mild to severe VMS at a time point (Week 12 (Baseline), 13, 14, ..., 64) is the average of the daily severity of available diary days in the corresponding 7-day window defined in Table 5.

A daily severity score of zero (0) is assigned if it is reported that no VMS occurred on that day. VMS data on the day of Week 64 visit is not used for the calculation of average daily VMS severity. If the count of available VMS data in a specific week is less than four (4), latest diaries in the previous window can be carried as needed to make 4 diaries available in this window. Then the average daily VMS severity in the week is calculated.

7.3.3.3 MENQOL scores deriving

The MENQOL is self-administered and consists of a total of 29 items in a Likert-scale format. Each item assesses the impact of one of four domains of menopausal symptoms, as experienced over the last month:

- vasomotor (items 1–3)
- psychosocial (items 4–10)
- physical (items 11–26)
- sexual (items 27–29)

Items pertaining to a specific symptom are rated as present or not present, and if present, how bothersome on a zero (not bothersome) to six (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 one to eight. (Hilditch JR, et al. 1996) Total MENQOL score will be calculated as the average of each domain score.

8. STATISTICAL METHODOLOGY

8.1 Study Subjects

8.1.1 Disposition of Subjects

The number of subjects who enter study A02 will be summarized (Table 14.1.1)

Subject disposition will be summarized for subjects completion status and discontinue reasons in tables for each treatment group of MT-8554-A01, and overall.

The data listing for Subject disposition will be generated.

8.1.2 Demographic and Other Baseline Characteristics

The subject demographic and baseline characteristic as below will be summarized by treatment group of MT-8554-A01, and overall in table and presented in data listing for the SAF population. (Table 14.1.2)

- Age (years)
- Sex
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- Menopausal status
- Antidepressant use
- Diabetic status
- Cardiovascular history
- Hypertension
- Heart Failure
- Baseline labs (creatinine, the estimated glomerular filtration rate [eGFR], haematocrit)
- Average daily VMS frequency
- Average daily VMS severity

If any of the above demographic and baseline characteristic are not collected at week 12 then the data collected in study MT-8554-A01 baseline will be used.

8.1.3 Medical History

The medical and surgical history will be summarized by treatment group of MT-8554-A01, and overall, SOC and PT in table and presented in data listing for the SAF population. (Table 14.1.3).

The count and percentage of subjects who had at least one medical history or surgical history will be presented. For each medical history or surgical history term, the count and percentage of subjects will be presented.

8.1.4 Concomitant Medications

The concomitant medications will be summarized in table by treatment group of MT-8554-A01, and overall and presented in data listing for the SAF population (Table 14.1.4).

The count and percentage of subjects who had at least one concomitant medication will be presented. For each concomitant medication term, the count and percentage of subjects will be presented.

Concomitant medications are medications that started prior to, on or after date of first dose of study A02 medication and ended on or after date of first dose of study A02 medication. This includes medications deemed as ongoing at the end of study.

As part of concomitant medication, prohibited medication will be listed.

8.1.5 Study Medication Exposure

Duration of exposure to study medication in days will be summarized in table and presented in data listing for the SAF population. (Table 14.1.5)

8.1.6 Treatment Compliance

Compliance to study medication will be presented for the ITT population in table. (Table 14.1.6)

All study medication administration and accountability data will be listed by subject.

8.1.7 Protocol Deviations

The major protocol deviations will be listed.

8.2 Safety Assessments

8.2.1 Adverse Events

The frequency and incidence of TEAEs will be summarized by System Organ Class (SOC) and Preferred Term (PT) by treatment of study A01 and overall.

Following summaries will be presented:

- Overall summary of TEAE (Table 14.3.1.1)
- TEAEs by SOC and PT (Table 14.3.1.2)
- TEAEs by SOC, PT and time of onset (Table 14.3.1.3)
- TEAEs by SOC, PT and severity (Table 14.3.1.4)
- TEAEs leading to discontinuation of study medication by SOC and PT (Table 14.3.1.5)
- Serious TEAEs by SOC and PT (Table 14.3.1.6)
- TEAEs by SOC, PT and relationship (Table 14.3.1.7)
- [redacted]

- Adverse drug reactions by SOC and PT (Table 14.3.1.9)
- Serious adverse drug reactions by SOC and PT (Table 14.3.1.10)
- TEAEs by SOC and PT for AEs with frequency >= 3% (or 5%) (Table 14.3.1.11)
- [redacted]

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

All AEs for each subject, including multiple occurrences of the same event, will be presented in full in a comprehensive listing including subject number, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop date and duration.

Deaths that occur during the study will be listed in a data listing. The data listings for serious TEAE and TEAE leading to discontinuation will be generated as well.

[redacted]

8.2.2 Laboratory Tests

For all continuous laboratory parameters, the lab values and change from baseline to post baseline visits are summarized by treatment group of A01 and overall and visit.

For all discrete laboratory parameters, the lab values are summarized with count and percentage by treatment group of A01 and overall and visit.

The lab tables will be generated for each Lab categories (Hematology, Biochemistry, Coagulation, Urinalysis and Hormones).

(Table 14.3.2.1, Table 14.3.2.2, Table 14.3.2.3, Table 14.3.2.4, Table 14.3.2.5)

All laboratory data will be listed with clinically relevant values flagged (L=Lower than lower limit of normal range or H=Higher than upper limit of normal range).

In addition, following clinical relevant ranges (and flags) will also be considered for summary table. The count and percent of subjects meeting the criteria will be presented. (Table 14.3.2.6)

- ALT $\geq 3 \times$ Upper Limit of Normal Range (ULN), 5× ULN, 8× ULN, 10× ULN
- AST and/or ALT $\geq 3 \times$ ULN, 5× ULN, 8× ULN, 10× ULN
- AST and/or ALT $\geq 3 \times$ ULN with Total bilirubin $\geq 2 \times$ ULN
- Total bilirubin $\geq 2 \times$ ULN
- Creatinine >= $2 \times$ ULN

The all clinical lab tests will be listed.

Table 6 Routine Laboratory Tests

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	
Urea	
Bilirubin (direct and total)	
Coagulation:	
Prothrombin time	Activated partial thromboplastin time
International normalized ratio	
Urinalysis:	
Specific gravity, pH, protein, glucose, ketones, urobilinogen, blood	
Microscopic examination[1]	
Reproductive hormones	
Luteinizing hormone (LH)	
Follicle stimulating hormone (FSH)	
Estradiol (E2)	

1. Performed only if required, based on urinalysis results.

8.2.3 Vital Signs

Vital signs data as below will be summarized descriptively in tables by treatment group of A01 and overall and scheduled visit (Table 14.3.3.1). All vital sign data will be listed.

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Pulse Rate (bpm)
- Tympanic Body Temperature (°C)
- Body Weight (kg)

8.2.4 ECGs

ECG parameters as below values and changes from baseline will be summarized descriptively by treatment group of A01 and overall and scheduled visit. (Table 14.3.3.2.1)

- PR (msec)
- RR (msec)
- QRS (msec)
- QT (msec)

- QTcF (msec)
- QTcB (msec)

For ECGs, number and percentage of subjects meeting the criteria listed below will be presented in tables (Table 14.3.3.2.2):

- QTc > 500ms
- QTc > 480ms
- QTc > 450ms
- Change from baseline in QTc > 30 msec
- Change from baseline in QTc > 60 msec
- These criteria will be applied to both QTcB and QTcF.

Shift tables will present the changes in clinically relevant categories from baseline to EOT/Early discontinuation visit. The categories are; "QTcB<=450msec", "QTcB >450 to <=480msec", "QTcB >480 to <=500msec", "QTcB >500msec". (Table 14.3.3.2.3)

Similar shift table will be also created for QTcF. The categories are; "QTcF<=450msec", "QTcF >450 to <=480msec", "QTcF >480 to <=500msec", "QTcF >500msec". (Table 14.3.3.2.4)

All ECG parameters and findings will be listed.

8.2.5 Physical Examinations

Physical examination data will be summarized descriptively in tables by treatment group of A01 and overall and visit (Table 14.3.4).

All physical examination data will be listed.

8.2.6 Breast Examination

The breast examination data will be summarized in tables by treatment group of A01 and overall and visit (Table 14.3.5). All breast examination data will be listed.

8.2.7 Endometrial Safety

All Endometrial safety data will be listed.

8.2.7.1 Endometrial Thickness Measured by Transvaginal Ultrasound (TVU)

The endometrial thickness as measured by TVU will be summarized in the tables by treatment group of A01 and overall and visit as below. (Table 14.3.6.1, Table 14.3.6.2)

1. Summary table presenting mean and SD for baseline, post baseline visits and change from baseline
2. Summary table of endometrial thickness by category (<5 mm, 5 to 8 mm, >8 mm)
3. Summary table for category of change from baseline (>3 mm, >5 mm)

The central reading data will be used for the analysis.

8.2.7.2 Endometrial Histology (Endometrial Biopsy)

The Endometrial biopsy data will be summarized in the tables by treatment group of A01 and overall and visit as below.

1. Summary tables of proportion of subjects in abnormal* category (Table 14.3.7.1)
2. Shift table for change in abnormal category from baseline to week 64 or EOT(Table 14.3.7.2)

*Note: The histological categories are based on 2003 draft FDA guidance. [redacted]

The data from adjudication committee will be used for the analysis.

8.2.8 Other Safety Assessments

Total score of 8-Item Patient Health Questionnaire (PHQ-8) and total score of the 7-item Generalized Anxiety Disorder questionnaire (GAD7) will be summarized descriptively in tables by treatment group of A01 and overall and scheduled visit. (Table 14.3.8, Table 14.3.9) The data listings will be generated.

8.3 Exploratory Assessments

All exploratory tests data will be listed.

Change from baseline in the average daily frequency of moderate to severe VMS will be summarized by treatment group of A01 and overall (Table 14.2.1).

Similar analyses will be conducted for VMS severity score. (Table 14.2.2).

The Plot of Mean change from baseline in VMS frequency and severity will be generated. (Figure 14.2.1, Figure 14.2.2). The Plot of observed mean values of VMS frequency and severity will be generated. (Figure 14.2.3, Figure 14.2.4).

The change from baseline in total and each domain score of the MENQOL will be summarized by treatment group of A01 and overall. (Table 14.2.3)

8.4 Dose Change

All subjects were treated with MT-8554 10 mg initially. Then from protocol amendment 4, all subjects remaining in study changed to MT-8554 5 mg. Some subjects already completed or discontinued the study. To compare the data before and after the dose change, the following analyses will be conducted.

No.	Title of Table	Analysis Population
14.1.5	Summary of Exposure to Study Medication: Duration of exposure the dose change	SAF
14.3.1.1	Summary of Treatment Emergent Adverse Events (TEAE)	SAF
14.3.1.1.Ex4Site	Summary of Treatment Emergent Adverse Events (TEAE -Exclude 4 Florida site-	SAF

No.	Title of Table	Analysis Population
14.3.1.2	Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term	SAF
14.3.1.2.Ex4Site	Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term -Exclude 4 Florida site-	SAF
14.3.1.4	Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity for before the dose change	SAF
14.3.6.1	Transvaginal Ultrasound (TVU)	SAF
14.3.6.1. Ex4Site	Transvaginal Ultrasound (TVU) -Exclude 4 Florida site-	SAF
14.3.6.2	Transvaginal Ultrasound (TVU) - Endometrial Thickness	SAF
14.3.6.2. Ex4Site	Transvaginal Ultrasound (TVU) - Endometrial Thickness -Exclude 4 Florida site-	SAF

8.5 Exploratory Analysis Excluding Some Study Sites

During the MT-8554-A01, the Sponsor observed a significant degree of study drug non-compliance at a few study sites, where some of these were clustered geographically and had study subjects duplication.

The Sponsor also observed 8 study sites (site number 104, 108, 112, 114, 119, 128, 144, and 158) with significant IP non-compliance based on MT-8554 PK levels. Among them, 4 sites (site number 104, 112, 114, and 119) had highest number of IP non-compliance based on PK levels, were among the high enrollers (site number 112 and 114 were top enrollers and 104 and 119 were among the top 8 enrollers), and were located at a close proximity to each other in the South Florida. The Sponsor initiated a comprehensive re-review to verify the operational conduct of the study.

The Sponsor's review team concluded that at these 4 Florida sites, training and monitoring was conducted similar to all other sites as per standards, and no concerns were identified by the study monitors during the conduct of the study. The Sponsor considered the possibility that the subjects' poor IP compliance could be due to early onset adverse events which might have prevented them from continuation of MT-8554. However, it was noted that there was a lack of adverse events reporting from these 4 Florida sites in comparison to the all others sites. The incidences of AEs at these 4 sites were 31.8, 37.0, 31.6 and 4.3% as compared to 44.1, 39.7, 49.3 and 64.3% at the other sites in placebo, 1, 5, and 10 mg groups respectively, in MT-8554-A01.

Of these 4 sites, one site was identified a duplicate subject during the screening period, which was dropped out of the study. The Sponsor conducted an additional database search to exclude unidentified duplicate subjects. The Sponsor identified 12 subjects at these 4 Florida sites, which were suspected of being duplicates based on date of birth, height, weight medical history, and medications. Later, all these 12 subjects were confirmed by the quality assurance review of the sites as being duplicates, at least one subject at each site.

Therefore, it was considered to conduct the statistical analyses without the data from these sites. As the exploratory analyses, the main efficacy and safety analyses specified as following list will be performed with the ITT and safety population excluding the 4 sites subjects.

No.	Title of Table	Analysis Population
14.1.1.Ex4Site	Subject Disposition and Analysis Population-Exclude 4 Florida site-	All Subjects
14.1.2.Ex4Site	Demography and Baseline Characteristics -Exclude 4 Florida site-	SAF
14.1.5.Ex4Site	Summary of Exposure to Study Medication: Duration of exposure -	SAF

No.	Title of Table Exclude 4 Florida site-	Analysis Population
14.1.6.Ex4Site	Summary of Compliance to Study Medication-Exclude 4 Florida site-	SAF
14.2.1.Ex4Site	Summary of VMS Frequency-Exclude 4 Florida site-	ITT
14.2.2.Ex4Site	Summary of VMS Severity-Exclude 4 Florida site-	ITT
14.2.3.Ex4Site	Summary of Menopause Specific Quality of Life (MENQOL) Domain and Total Scores-Exclude 4 Florida site-	ITT
14.3.1.1.Ex4Site	Summary of Treatment Emergent Adverse Events (TEAE) -Exclude 4 Florida site-	SAF
14.3.1.1.A.Ex4Site	Summary of Treatment Emergent Adverse Events (TEAE) for before the dose change -Exclude 4 Florida site-	SAF
14.3.1.1.B.Ex4Site	Summary of Treatment Emergent Adverse Events (TEAE) for after the dose change -Exclude 4 Florida site-	SAF
14.3.1.2.Ex4Site	Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term-Exclude 4 Florida site-	SAF
14.3.1.2.A.Ex4Site	Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term for before the dose change-Exclude 4 Florida site-	SAF
14.3.1.2.B.Ex4Site	Incidence of Treatment Emergent Adverse Events by System Organ Class, Preferred Term for after the dose change-Exclude 4 Florida site-	SAF
14.3.6.1.Ex4Site	Transvaginal Ultrasound (TVU) -Exclude 4 Florida site-	SAF
14.3.6.2. Ex4Site	Transvaginal Ultrasound (TVU) - Endometrial Thickness-Exclude 4 Florida site-	SAF
14.3.7.1. Ex4Site	Endometrial Biopsy -Exclude 4 Florida site-	SAF

9. DATA PRESENTATION CONVENTIONS

9.1 Number of Digits to Report

Table 7 Number of decimal places (DP) or significant digits (SD)

Statistic	Specification	Apply to
Minimum, maximum	same number of DPs as the data provided in the datasets	All original, i.e. non-derived, data provided in the datasets
	See section 7.3	All derived data
Mean, Median	one more DP than above	All
SD, SE	two more DP than above	All
Percentages*	1 DP	All

*Percentages: use 1 place beyond the decimal point, except for the following cases:

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

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

Listings will be presented in subject, visit (where applicable) and date (where applicable) order. Listings will be produced (landscape in MS Word) using PROC REPORT in SAS monospace font and pitch 8.

Summary tabulations will be presented by treatment group of study A01 and overall if appropriate, scheduled visit order (if appropriate). Continuous data summaries will present (unless stated otherwise) number of observations, mean, standard deviation, median, minimum and maximum. Categorical data summaries will present the number of observations and the corresponding percentage.

10. CHANGE FROM THE PROTOCOL

Protocol says "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.". However, the baseline VMS severity score is from the end of treatment of study A01. The VMS severity score there is defined as (1xFmi + 2xFmo + 3xFse)/(Fmi + Fmo + Fse). So this formula is used for baseline VMS severity score in A02.

11. SOFTWARE

The statistical evaluation will be performed using SAS® Version 9.4 or later.