Statistical Analysis Plan

Protocol Number: MT-2990-A01

A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of MT-2990 in Women with Endometriosis Experiencing Endometrial Related Pain

Version Number: 01
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Prepared By:	Mitsubishi Tanabe Pharma Development America, Inc.
Version:	V01
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APPROVAL FORM

Statistical Analysis Plan

Protocol No.	MT-2990-A01
Protocol Title	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of MT-2990 in Women with Endometriosis Experiencing Endometrial Related Pain
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ABBREVIATIONS

Abbreviations	Definitions
AE	adverse event
AESI	adverse events of special interest
ANCOVA	Analysis of covariance
CRF	case report form
[redacted]	[redacted]
BL	Baseline
BMI	Body mass index
DMC	data monitoring committee
ECG	electrocardiogram
[redacted]	[redacted]
EOS	end of study
EOT	end of treatment
[redacted]	[redacted]
GCP	Good clinical practice
HDL	High-density lipoprotein
ICH	International council for clinical harmonization
ISA	interim safety assessment
ITT	intent-to-treat
LS Mean	Least square mean
MedDRA	medical dictionary for regulatory activities
MMRM	Mixed effect model repeated measure
[redacted]	[redacted]
PK	pharmacokinetics
PP	per protocol
PT	preferred term
RAND	randomized
SAF	safety
SAP	statistical analysis plan
SD	standard deviation
SE	Standard error
SOC	system organ class
TEAE	treatment emergent adverse event
[redacted]	[redacted]
ULN	Upper limit of normality
WHO	World health organization

[redacted]

[redacted].

1. INTRODUCTION

This statistical analysis plan (SAP) is based on the protocol amendment 4 dated 04 Mar. 2020. The plan covers statistical analysis, tabulations and listings of the study.

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

2. STUDY OBJECTIVE AND ENDPOINTS

Overall, the objective of the study is to evaluate the safety and efficacy of MT-2990 in patients with surgically diagnosed endometriosis, experiencing moderate to severe endometriosis related pain and impact on quality of life. In addition, the study will assess the effects of MT-2990 [redacted]

2.1. Study Objectives

2.1.1. Primary Objective

- To assess the efficacy of MT-2990 on the nonmenstrual pelvic pain in women with endometriosis

2.1.2. Secondary Objectives

- To assess the efficacy of MT-2990 on the dysmenorrhea in women with endometriosis
- To assess the effect of MT-2990 on the dyspareunia
- To assess the safety and tolerability of MT-2990

2.1.3. [redacted]

- [redacted]
- [redacted]
- [redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoint

- Mean change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]

2.2.2. Key Secondary Efficacy Endpoint

- Mean change from Baseline through Week 16 in dysmenorrhea [redacted]

2.2.3. Secondary Efficacy Endpoints

- Mean change from Baseline through Week 16 in dyspareunia score [redacted]
- Mean change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean change from Baseline through Week 16 in dyspareunia score [redacted]
- Mean change from Baseline through Week 16 in pill count of any rescue analgesic use
- Mean change from Baseline through Week 16 in opioid pill count
- Time to rescue medications
- Percentage of nonmenstrual pelvic pain responders through Week 16 [redacted]
- Percentage of dysmenorrhea responders through Week 16 [redacted]
- Percentage of dyspareunia responders through Week 16 [redacted]
- Mean percentage change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean percentage change from Baseline through Week 16 in dyspareunia [redacted]
- Percentage of nonmenstrual pelvic pain responders through Week 16 [redacted]
- Percentage of dysmenorrhea responders through Week 16 [redacted]
- Percentage of dysmenorrhea responders through Week 16 [redacted]
- Mean percentage change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean percentage change from Baseline through Week 16 in dyspareunia [redacted]
- Number and percentage of women who responded [redacted]
- Mean change from Baseline through Week 16 on [redacted]
- Number and percentage of women who responded "[redacted]

2.2.4. Safety Assessments

- Physical examination (including breast examination)
- Vital signs (blood pressure, pulse rate, 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)
- Treatment emergent adverse events (TEAEs)

[redacted]

3. STUDY DESIGN

3.1. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study, stratified by moderate or severe pain to evaluate safety and efficacy of MT-2990 in women with endometriosis-associated moderate to severe pain.

[redacted]

[redacted]

Following the Screening period, eligible subjects who have met all the eligibility criteria and have moderate or severe nonmenstrual pelvic pain, and dysmenorrhea will be randomized into the study. Approximately 38 subjects per arm will be enrolled. Subjects will be randomly allocated to 1 of 2 treatment groups (placebo or MT-2990 [redacted]) in a ratio of 1:1. A single [redacted] dose of placebo or [redacted]

End-of-treatment (EOT) will occur at Week 12 (Visit 7) and primary and secondary efficacy endpoints will be assessed at the Week 16 (Visit 9) visit. Subjects who discontinue from the study will complete the procedures for Visit 9 within 10 days of discontinuation (or as soon as possible after the site becomes aware of the discontinuation).

During the Extended Follow-up period, visits will be conducted via a telephone call at Week 27 (Visit 10) and at Week 38 (Visit 11). Visit 11 will be the end of study (EOS) visit.

The Sponsor will be unblinded after Week 16 (Visit 9), while the Sites and subjects will remain blinded until the end of the Extended Follow-up period at Week 38 (Visit 11). During the study, database will be locked twice; Week 16 (Visit 9) to assess safety and efficacy, and at Week 38 (Visit 11) to assess other outcomes during the Extended Follow-up period.

The study design schema is presented in.

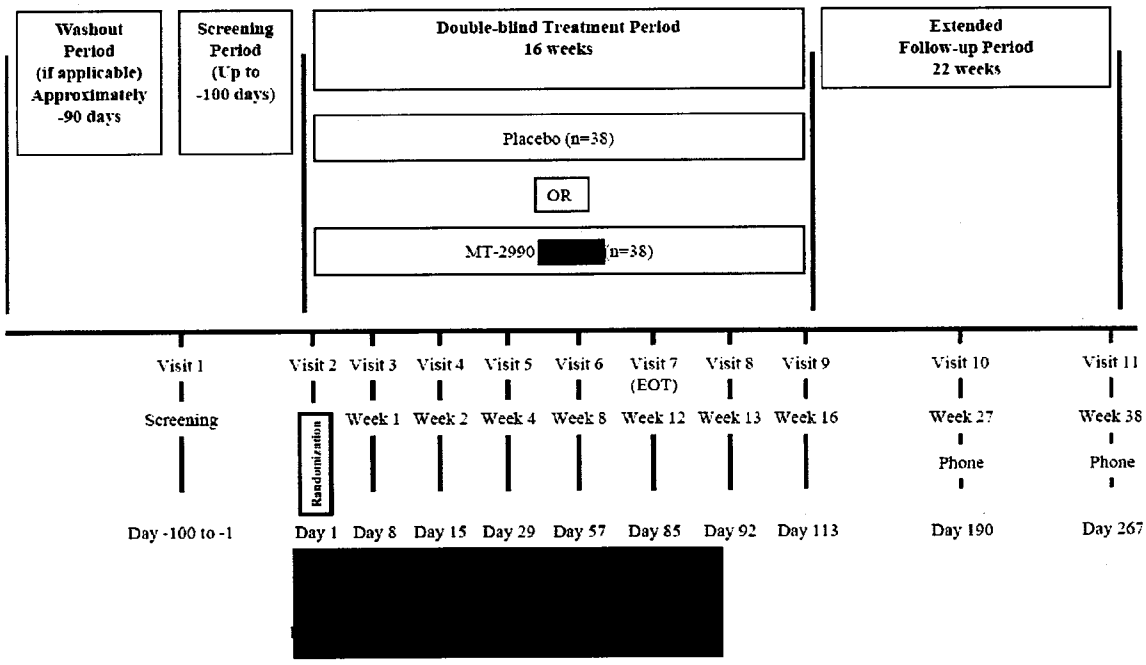
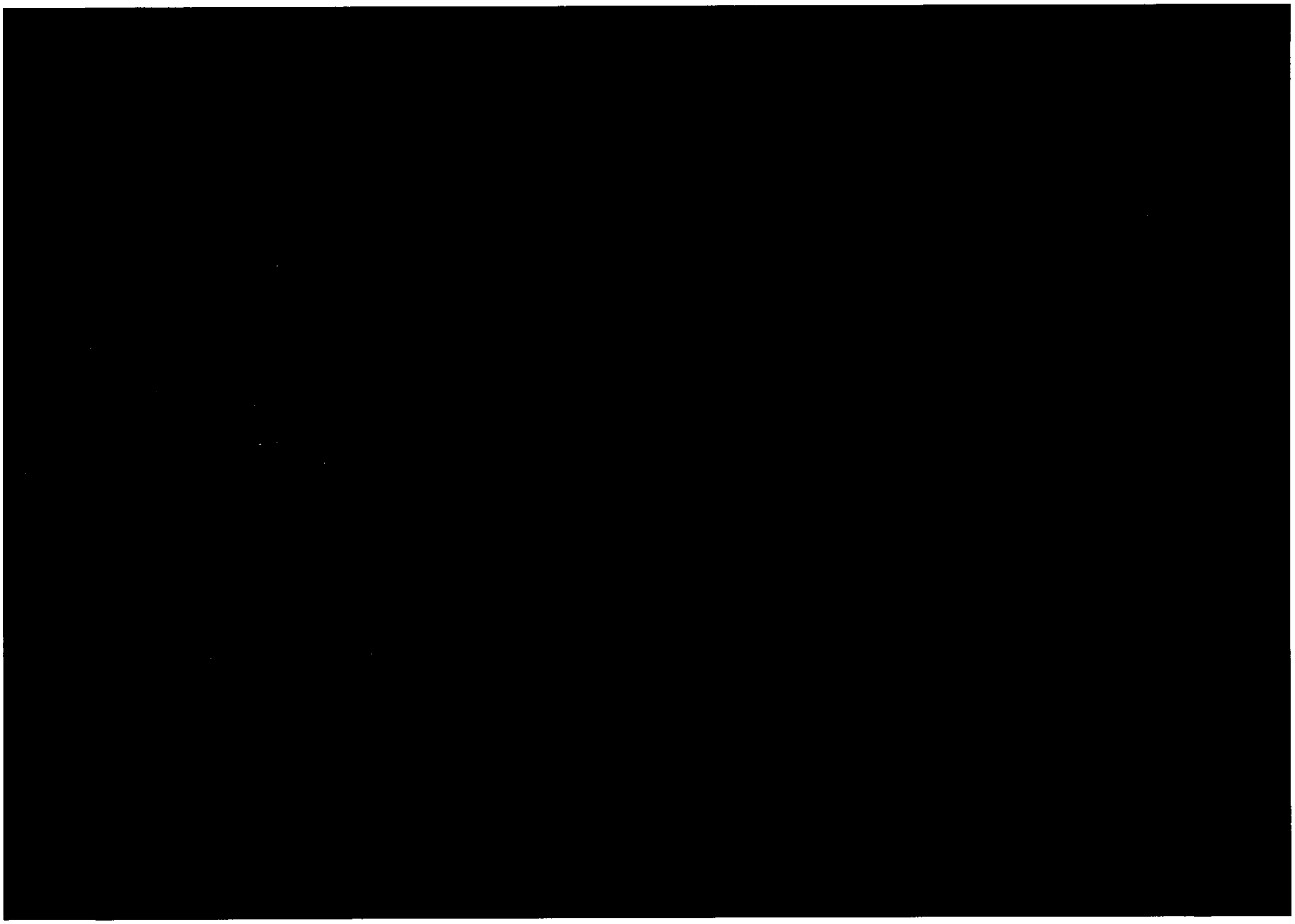
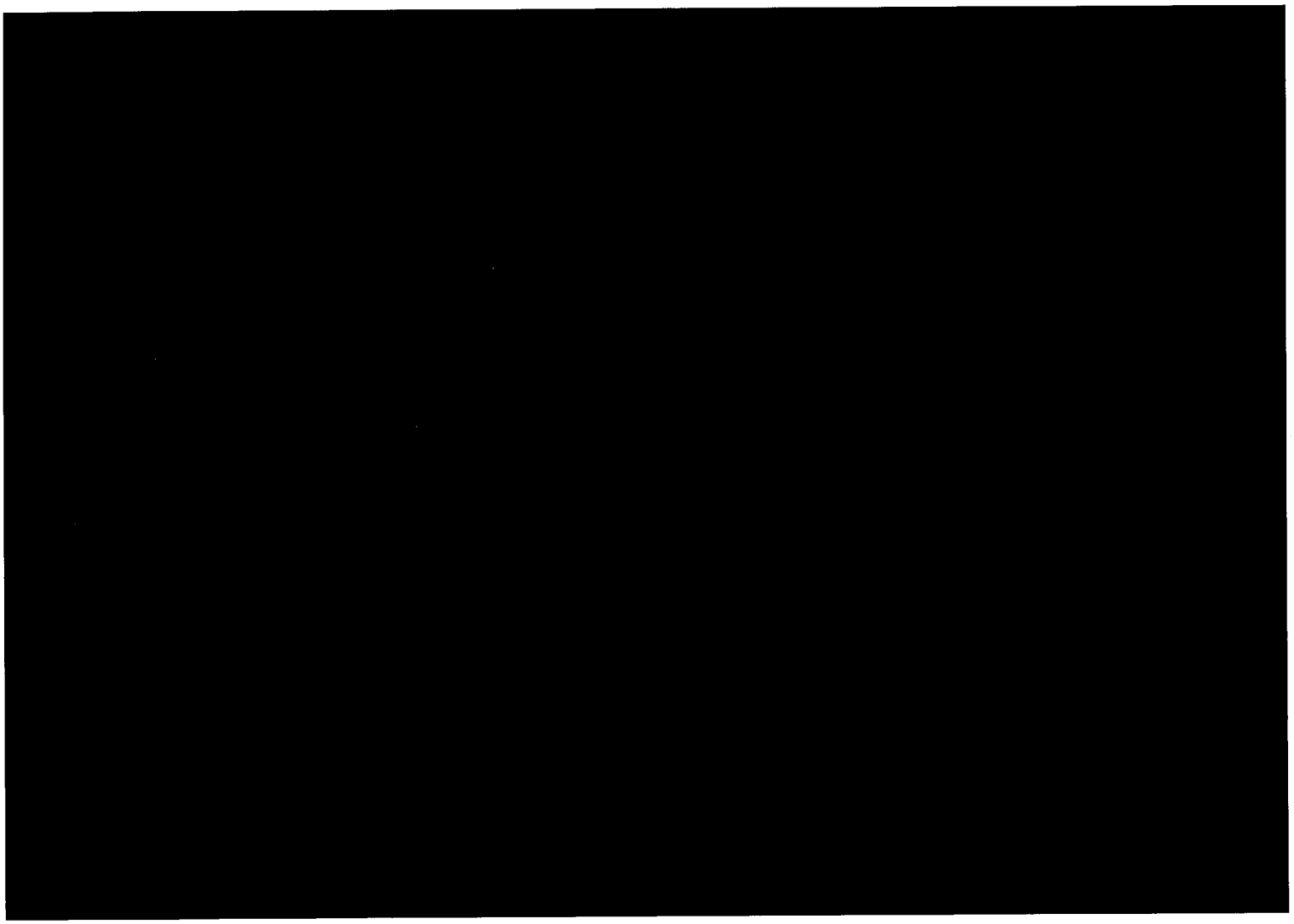
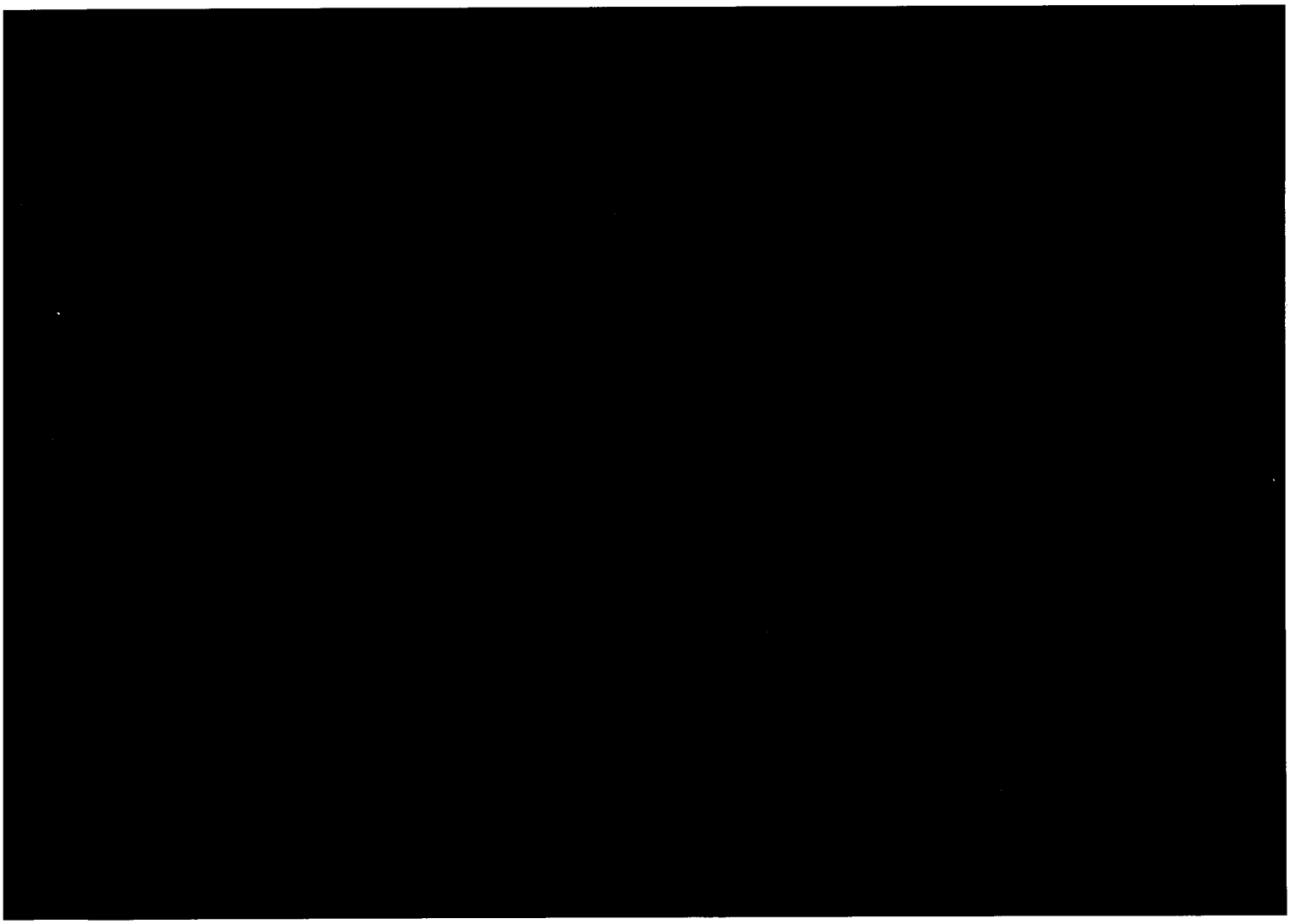


Figure 1 Study design schema







3.3. Determination of Sample Size

Power analysis for sample size calculation was performed under 2-sample t-test at the 5% level of significance to identify significance of the difference between MT-2990 and placebo on the mean change from Baseline through Week 16 in nonmenstrual pelvic pain. A total of 28 subjects per arm will provide at least 80% power for detecting a clinically meaningful difference (placebo versus treatment) of -0.5 in the mean change from Baseline in nonmenstrual pelvic pain and a standard deviation (SD) of 0.65, [redacted] As this study is exploratory study (proof of concept study), multiplicity for multi-endpoint is not considered. Assuming a drop-out rate of 25%, a total of 76 subjects (38 subjects per arm) are planned to be randomized in this study.

4. PLANNED ANALYSIS

4.1. Interim Safety Assessment

There will be 3 interim safety assessments. The first interim assessment for safety will be performed when 20 subjects are randomized and have completed the Week 2 visit. The second interim assessment for safety will be performed when 50% of the subjects are randomized and have completed the Week 4 visit. The third interim assessment for safety will be performed when 50% of the subjects are randomized and have completed the Week 16 visit.

4.2. Final Analysis

Final data analysis will be conducted after database lock.

4.3. Data Monitoring Committee (DMC)

An independent DMC, composed of experts in the management of subjects with the disease under study will be established for MT-2990-A01 according US FDA guidance. An independent biostatistician will be assigned to the DMC to maintain the integrity of the study blind and provide safety data at regular predefined intervals during the study and provide the interim safety assessments to the DMC.

The primary purpose of this committee will be to review safety data for the protection of subject safety (including infusion site reactions, hypersensitivity and immune system disorders such as allergic reaction, anaphylaxis, cytokine release syndrome, etc).

There will be 3 interim safety assessments as described in section 4.1. The planned interim safety assessments will be conducted to determine whether the study will be stopped due to safety concerns.

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

the study.

5. ANALYSIS POPULATIONS

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

- Randomized (RAND) population:
  Will include all randomized subjects.
- Safety (SAF) population:
  Will include all randomized subjects who received at least 1 dose of study medication.
- Intent-to-treat (ITT) population:
  Will include all randomized subjects who received at least 1 dose of study medication and have at least 1postscreening efficacy assessment.
- Per-protocol (PP) population:
  Will include all ITT subjects who do not have any important protocol deviations and have completed the Double-blind Treatment period.
- Pharmacokinetics (PK) population:
  Will include all randomized subjects who received at least 1 dose of MT-2990 and have at least 1 postdose value for serum concentration without important protocol deviations which may affect the PK of MT-2990.
- [redacted]
- [redacted]
- Pharmacodynamics (PD) population:
  Will include all randomized subjects who receive at least 1 dose of study medication and had at least 1 post–dose PD assessment and for whom the PD data are considered to be sufficient and interpretable.

Important protocol deviations will be identified and documented during a data review prior to database lock and confirmed by database lock.

6. STATISTICAL CONSIDERATIONS

6.1. Descriptive Statistics

(1) Non-PK related

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

(2) PK related

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

6.2. Statistical Tests

Unless otherwise specified, all formal statistical tests of treatment effects will be done at two-sided significance level of 0.05. Point estimates will be accompanied with two-sided 95% confidence intervals where applicable.

7. DATA CONVENTIONS

7.1. Analysis Variable Definitions

7.1.1. Study Subjects

7.1.1.1. Demographic and Other Baseline Characteristics

(1) Age

Age will be calculated as the integer difference in years from date of birth to informed consent date.

(2) BMI

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

BMI (kg/m^2) = weight at Day 1 (kg) / {height (m)}^{2}

(3) Years from initial diagnosis

Years from initial diagnosis will be derived from record of subject's medical history which has a value of "Endometriosis". Calculation will be done on a year part of the record as below.

Years from initial diagnosis = Year of first diagnosis of Endometriosis – Year of informed consent date

7.1.1.2. Treatment Duration and Compliance

(1) Treatment Duration

Treatment Duration (days) = the latest date of (last visit in Double-blind Treatment Period or discontinuation in Double-blind Treatment Period) – first dose date + 1

(2) Treatment Compliance

The subjects are supposed to take a dose every four weeks and totally 4 doses per protocol.

Treatment compliance (%) =number of doses/ROUNDUP(treatment duration/28).

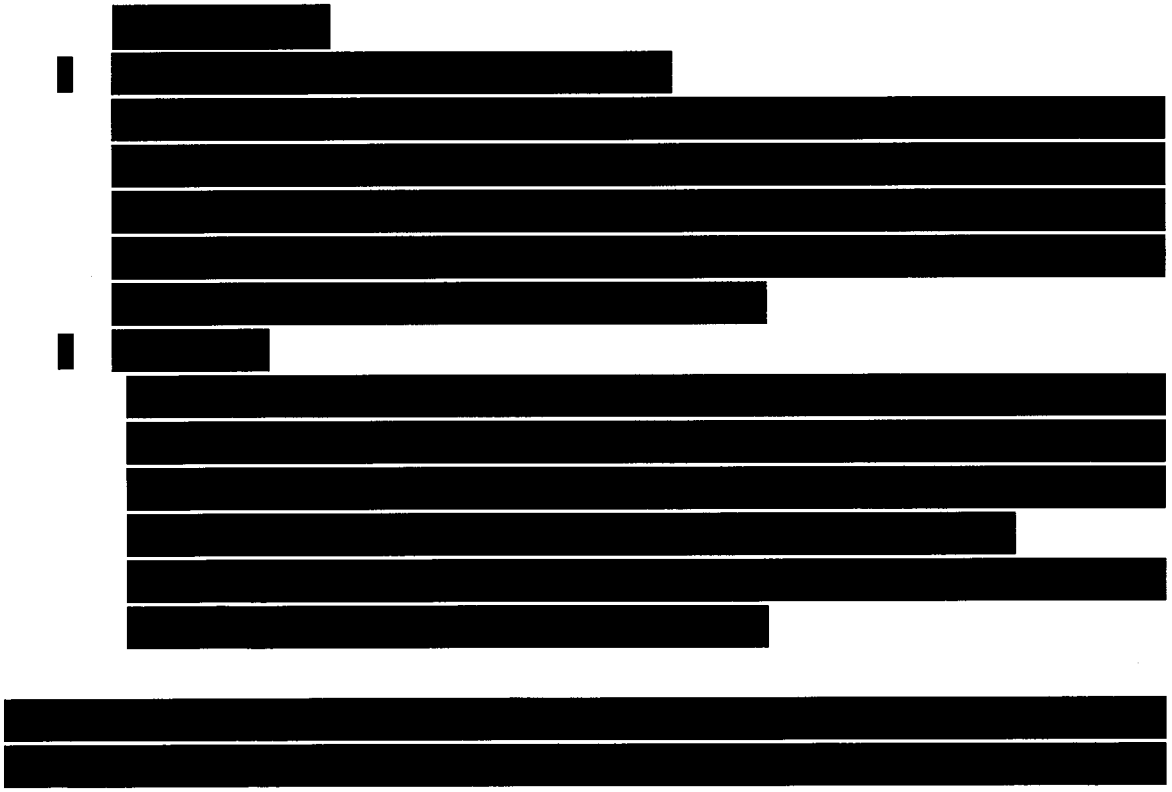
7.1.2. Efficacy assessments

7.1.2.1. Baseline Definitions

The baseline value for assessments using e-Diary will be based on the average of the last 35 calendar days during the screening period. For assessments that are measured for the first time on Study Day 1, use the Study Day 1 results for the baseline value. The Baseline value for other variables is defined as the last non-missing value prior to first dose of the study drug unless otherwise specified.

All baseline efficacy data will not be imputed, unless otherwise specified.

7.1.2.2. Pain assessment of nonmenstrual pelvic pain, dysmenorrhea and dyspareunia



be calculated.

7.1.2.3. [redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.2.5. Other assessment using e-Diary data

- Pill count of any rescue analgesic used

  [redacted]

- Opioid pill count

  [redacted]

- Number of days with any rescue analgesic use

  [redacted]

- Number of days with opioid use

  [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.1.3. Safety Assessments

7.1.3.1. Adverse Events

Adverse events will be coded according to the MedDRA version 21.1

(1) Treatment Emergent Adverse Events (TEAEs)

AEs are considered as treatment emergent if they newly occur after the first dose administration of study medication or if a predose event increases in severity following dosing.

(2) Adverse Events of Special Interest (AESI)

All fractures.

7.1.3.2. 12-Lead ECGs

(1) Criteria for pre-defined limit

- post-baseline QTcF > 450 msec
- Baseline QTcF < 450msec and post-baseline QTcF > 450msec, 480msec, 500msec
- Change from baseline QTcF > 30msec, 60msec

7.1.4. Pharmacokinetics Evaluation

[redacted]

[redacted]

[redacted]

(3) Safety endpoints

- Adverse events (AE):

  If severity/relationship is found to be missing, the most severe/reasonable possibility will be imputed respectively for the summary of interest.

  For AE start and/or end date missing or partial dates, the AE will be treated as TEAE if it cannot be determined as a non-TEAE.

- Other safety data:

  For safety summaries, only observed data will be used. Unless otherwise specified. Missing safety data will not be imputed.

[redacted]

7.3. Analysis Visit Definitions

(1) Efficacy endpoints derived from e-diary data

Analysis visit window for assessments using e-Diary will be based on the study day of the [redacted] specific visit. The analysis visits and windows are defined as the following.

Analysis visit	Study Day of Monthly PGIC Assessments	Window (W_x)
Baseline	NA	Last 35 days prior to Day 1
Week 4	X_1	$max(1, X_1 - 35) < W_4 \leq X_1$
Week 8	X_2	$max(X_1, X_2 - 35) < W_8 \leq X_2$
Week 12	X_3	$max(X_2, X_3 - 35) < W_{12} \leq X_3$
Week 16	X_4	$max(X_3, X_4 - 35) < W_{16} \leq X_4$

The date of the first dose of study drug is defined as Day 1. If monthly [redacted] assessment is missing, following rules will be applied to impute a study day.

- If the date of [redacted] assessment at Week 4 is missing, the date of vital sign assessment will be set as the study day. If the date of vital sign assessment is missing, the study day is set to be 28.
- If the date of [redacted] assessment at Week 8, 12, or 16 is missing, the date of vital sign assessment will be set as the study day. If the date of vital sign assessment at Week 8, 12, or 16 is missing, the study day is set to be the preceding month's day + 28.

The window for [redacted] assessment is defined in following section.

(2) Other endpoints

The analysis visits will be defined as following.

Analysis visit	Nominal day	Window
Baseline	Day 1	NA
Week 1	Day 8	Day 2 to 11
Week 2	Day 15	Day 12 to 20
Week 4	Day 29	Day 21 to 43
Week 8	Day 57	Day 44 to 71
Week 12 (EOT)	Day 85	Day 72 to 88
Week 13	Day 92	Day 89 to 99
Week 16	Day 113	Day 100 or after
Week 27	Day 190	NA
Week 38 (EOS)	Day 267	NA

EOT assessment data will be included as visit data in the applicable window.

The date of the first dose of study drug is defined as Day 1. If the data at Day 1 is missing, the last data before Day 1 will be used for baseline. If one visit corresponds to both window of

week 12 and 13, the visit will be applied an analysis visit which matches visit on case report form (CRF). For other visits, if there are multiple data in a window, the closest data to nominal day will be used. If more than one data in the window with the same distance to the nominal day, the data of later date will be used. For Week 27 and 38, CRF visit will be used as analysis visits.

8. STATISTICAL METHODOLOGY

8.1. Study Subjects

8.1.1. Subject Disposition

Subject disposition will be summarized on the RAND population.
Subject disposition will be listed on the RAND population.

8.1.2. Analysis Population

Analysis populations will be summarized by treatment group. Analysis populations will be listed on the randomized population.

8.1.3. Number of subject screened

The number of subjects screened will be summarized and listed.

8.1.4. Demographic and Other Baseline Characteristics

The following demographic and other baseline characteristics will be used.

	Category	Descriptive
Age		Yes
Sex	Female	Yes
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown	Yes
Race	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Other	Yes
Height (cm)		Yes
Weight at Day 1 (kg)		Yes
BMI (kg/m^2)		Yes
Baseline nonmenstrual pelvic pain		Yes
Baseline dysmenorrhea		Yes
Baseline dyspareunia score		Yes

Usage of analgesic agents	[redacted]	[redacted]
[redacted]		Yes
Years from initial diagnosis		Yes

Demographic and other baseline characteristics will be summarized on the SAF and ITT population.

Demographic and other baseline characteristics will be listed on the RAND population.

If several kinds of race are selected in the eCRF, it is treated as 'Multiple' in SDTM.

Medical history will be summarized and listed on the SAF population.

8.1.5. Treatment Duration and Compliance

Treatment duration and compliance will be summarized on the SAF and ITT population.

Treatment duration and compliance will be listed on the RAND population.

8.1.6. Concomitant Medication

Concomitant medication will be summarized in table and listed on the SAF population.

Prohibited medication will be listed on the SAF population.

8.2. Efficacy Assessments

All efficacy analyses will be performed on ITT population. All applicable endpoints are summarized.

8.2.1. Primary Efficacy Endpoint

Mean change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted] will be analyzed in table.

As the Primary analysis, Change from Baseline through Weeks 4, 8, 12, and 16 in the mean scores of nonmenstrual pelvic pain will be analyzed using a repeated measures analysis of covariance model with an unstructured covariance structure. The analysis model will include Baseline value of the endpoint and baseline value*treatment as a covariate; weeks, treatment and weeks*treatment as fixed effect; subjects as random effect. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom. Point estimates and 95% CIs for the difference between each active dose and placebo at Week 16 and other time points will be obtained. In the event that this analysis model fail to converge, ARH(1), AR(1), CS correlation matrix will be used sequentially.

The primary efficacy analysis will be also performed on PP population.

As the secondary analysis, the primary analysis will be conducted for the primary endpoint with the last observation carried forward method for imputing the missing value at or before the Week 4, 8, 12 and 16.

The primary efficacy endpoint data will be listed.
The plot of LS mean of change from baseline value (and SE as error bar) of nonmenstrual pelvic pain [redacted] will be generated.
The plot of LS mean percentage change from baseline value (and SE as error bar) of nonmenstrual pelvic pain [redacted] will be generated.

8.2.2. Key Secondary Efficacy Endpoints

Similar analysis to the primary analysis will be conducted for the key secondary endpoint that will report as numeric data.

- Mean change from Baseline through Week 16 in dysmenorrhea [redacted]

8.2.3. Secondary Efficacy Endpoints

Similar analysis to the primary analysis will be conducted for the secondary endpoints that will report as numeric data.

- Mean change from Baseline through Week 16 in dyspareunia score [redacted]
- Mean change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean change from Baseline through Week 16 in dyspareunia score [redacted]
- Mean change from Baseline through Week 16 in pill count of any rescue analgesic use
- Mean change from Baseline through Week 16 in opioid pill count
- Mean change from Baseline through Week 16 in number of days with any analgesic use
- Mean change from Baseline through Week 16 in number of days with opioid use
- Percentage of nonmenstrual pelvic pain responders through Week 16 [redacted]
- Percentage of dysmenorrhea responders through Week 16 [redacted]

- Percentage of dyspareunia responders through Week 16 [redacted]
- Mean percentage change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean percentage change from Baseline through Week 16 in dyspareunia [redacted]
- Percentage of nonmenstrual pelvic pain responders through Week 16 [redacted]
- Percentage of dysmenorrhea responders through Week 16 [redacted]
- Mean percentage change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline through Week 16 in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean percentage change from Baseline through Week 16 in dysmenorrhea [redacted]
- Mean percentage change from Baseline through Week 16 in dyspareunia [redacted]
- Mean percentage change from Baseline through Week 16 in dyspareunia [redacted]
- Number and percentage of women who responded [redacted]
- Mean change from Baseline to Weeks 4, 8, 12, and 16 [redacted]
- Number and percentage of women who responded [redacted]

[redacted]

Time to rescue medications is defined as the number of days from Day 1 to the first use of a rescue medication during the treatment period for patients who did not take rescue medications in the last 35 calendar days during the screening period.

Time to rescue medications will be analyzed using a log-rank test, and significance difference test based on Restricted Mean Survival Time. Same analyses will be conducted for time to hospitalization and time to surgeries.

The logistic regression model will be used to analyze the response rate (percentage) based on nonmenstrual pelvic pain [redacted]. Odds ratio and risk ratios for the percentage of responders will be calculated. The analysis model will include categorization of "response" and "no response" as the dependent variable, treatment arm as the main effect, and the Baseline score for nonmenstrual pelvic pain as the covariate. This analysis will be conducted using observed case and last observation carry forward (LOCF) respectively. The last observation carried forward method will be used for the missing value at or before Week 16.

In addition, this analysis will be conducted to dysmenorrhea pain responders and dyspareunia pain responders in the same way. And, in each responder modified by analgesic use analyses will be repeated in the same way.

[redacted]

The plot of LS mean of change from baseline value (and SE as error bar) of dysmenorrhea and dyspareunia score will be generated.

The plot of LS mean percentage change from baseline value (and SE as error bar) of dysmenorrhea and dyspareunia score will be generated.

The ROC curve of cutoff numbers for clinical responder based on nonmenstrual pelvic pain, dysmenorrhea and dyspareunia score [redacted] scale will be generated.

Responder modified by analgesic use analyses will also be performed by subgroups described as below. This subgroup analysis will be performed on Week 12 and Week 16 values.

Subgroup	Category
Age	$< 25, \geq 25 \; and \leq 35, > 35$
Race	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not

	Reported, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown
Baseline pain score for DYS	< Median of Baseline pain score for DYS ≥ Median of Baseline pain score for DYS
Baseline pain score for NMPP	< Median of Baseline pain score for NMPP ≥ Median of Baseline pain score for NMPP
Baseline pain score for dyspareunia	< Median of Baseline pain score for dyspareunia ≥ Median of Baseline pain score for dyspareunia
Baseline analgesic use	[redacted]
Time since diagnosis	$< 2, \geq 2$ *and* $< 5, \geq 5$

[redacted]

8.3. Safety Assessments

Safety assessments will be made on the SAF population.

8.3.1. Adverse Events

Overall summary for the following will be conducted.

- Subjects with at least one TEAE
- Subjects with at least one serious TEAE
- Subjects with at least one TEAE leading to study medication discontinuation
- Subjects with at least one treatment emergent AESI
- Subjects with TEAE leading to death

According to protocol, all fractures will be collected as adverse events of special interest (AESI).

The following summaries also will be conducted.

- TEAEs by SOC and PT
- Serious TEAEs by SOC and PT
- TEAEs Leading to Study Treatment Discontinued by SOC and PT
- Treatment Emergent AESI by SOC and PT
- TEAEs by SOC, PT and severity
- TEAEs by SOC, PT and relationship to study medication

Each of the summaries will be done at the subject level - multiple occurrences of the same event within a subject will be counted once in the summaries by SOC and PT; multiple occurrences of the same event within a subject will be counted once in the maximum severity category (severe > moderate > mild) and/or maximum drug relationship category (reasonable possibility/no reasonable possibility).

The following will be listed.

- TEAEs
- Serious TEAEs
- TEAEs leading to study medication discontinuation
- Treatment emergent AESI
- Death

8.3.2. Laboratory Tests

Absolute values and changes from baseline will be summarized for the following laboratory tests parameters.

Laboratory Test	Parameters
Hematology	Hemoglobin*, Hematocrit*, Platelet count*, Red blood cell (RBC) count*, Reticulocyte count*, Mean corpuscular hemoglobin (MCH),

	Mean corpuscular hemoglobin concentration (MCHC), Mean corpuscular volume (MCV), White blood cell (WBC) count and differential
Biochemistry	Alkaline phosphatase (ALP) *, Aspartate aminotransferase (AST) *, Alanine aminotransferase (ALT) *, Gamma-glutamyl transpeptidase (GGT) *, Potassium*, Sodium*, Chloride*, Inorganic phosphate, Glucose*, Urea, Bilirubin (direct and total) *, Cholesterol*, Triglycerides*, High density lipoprotein-cholesterol (HDL-C) *, Low density lipoprotein-cholesterol (LDL-C) *, Protein (total) *, Albumin*, Creatine kinase*, Creatinine*
Coagulation	Prothrombin time*, International normalized ratio*, Activated partial thromboplastin time*
Urinalysis	Specific gravity, pH*, protein*, glucose*, ketones*, urobilinogen*, haemoglobin

Only the parameters with * will be summarized for interim safety assessment.

Shift table for urinalysis will be generated if it is needed.

All data will be listed.

8.3.3. Vital Signs

Absolute values and changes from baseline will be summarized for the following parameters.

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Body Temperature (°C)

All data will be listed.

8.3.4. 12-Lead ECGs

Absolute values and changes from baseline will be summarized for the following parameters.

- Heart Rate (bpm)
- PR (msec)
- QRS (msec)
- QT (msec)
- QTcF (msec)
- QTcB (msec)

The percentage of subjects with 12-lead ECG values outside pre-defined limit will be summarized.

All data will be listed.

8.3.5. Physical Examinations

Physical examination will be listed.

8.4. Pharmacokinetics Evaluation

Pharmacokinetics evaluation will be made on the PK population.

8.4.1. Serum MT-2990 Concentration

Serum MT- 2990 concentrations will be summarized at each nominal sampling point (Table 14.4.1). All serum concentrations will also be listed.

[redacted]

[redacted]

8.5.2. Pharmacodynamics Evaluation

Pharmacodynamics evaluation will be made on the PD population.

[redacted]

9. DATA PRESENTATION CONVENTIONS

9.1. Number of Digits to Report

(1) Non-PK related

Statistic	Specification	Apply to
Minimum, Maximum	Same number of DPs as the data provided in the datasets	All original (i.e. non-derived)
	See section 7.1	Derived
Mean, Median, SD, SE, Confidence intervals	One more DP than above	All
Percentages[*1]	1 DP	All
Ratios	3 DPs	All
p-values[*2]	3 DPs	All

[*1] 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

[*2] p-values: use 3 places beyond the decimal point, except for the following cases:

If the p-value is less than 0.001, then use p<0.001

Note: DPs for specific parameters are regarded as follows.

[PARAMCD (Conversion factor)]

- 2 DPs
  CHOL (0.02586), HDL (0.02586), LDL (0.02586), TRIG (0.01129),
  PHOS (0.3229), UREAN (0.357)
- 1 DP
  GLUC (0.0555), BILDIR (17.1), BILI (17.1)
- Integer
  CREAT (88.4)

(2) PK Serum Concentration

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

9.2. Treatments to Report

Treatment	For TFLs
Placebo	Placebo
MT-2990 [redacted]	MT-2990 [redacted]

[redacted]

(2) Safety

Analysis Visit	Apply to		
	Laboratory Tests	Vital Signs	12-Lead ECGs
Baseline	X	X	X
Week 1	X	X	
Week 2	X	X	
Week 4	X	X	
Week 8	X	X	
Week 12 (EOT)	X	X	
Week 13	X	X	
Week 16	X	X	X
Week 27			
Week 38 (EOS)			

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

In by-visit summary tables for interim safety assessment, limited analysis visits will be reported. The first interim safety assessment will report baseline to Week 2. The second interim safety assessment will report baseline to Week 4. The third interim safety assessment will report baseline to Week 16. All visit will be included in the data listing.

10. CHANGE FROM THE PROTOCOL

The following endpoints are removed.

- Mean change from Baseline through Week 16 for endometriosis-associated pain
  This endpoint will be removed as it is a duplicate of other endpoints.

The following endpoints will be added.

- Mean change from Baseline through Week 16 in number of days with any analgesic use
- Mean change from Baseline through Week 16 in number of days with opioid use

In order to evaluate the status of use of rescue medication the above two endpoints are added.

11. SOFTWARE

All statistical analyses will be performed using SAS version 9.4 or higher.

12. REFERENCES

N/A