Protocol

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: Amendment 4, Version 5.0
Date: 04 March 2020
NCT number: NCT03840993

STUDY PROTOCOL

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

IND Number:	139702
Investigational Medicinal Product:	MT-2990
Indication:	Treatment of moderate to severe endometriosis-related pain in women with surgically diagnosed endometriosis
Sponsor:	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310
Original Protocol Version, Version 1.0:	31 July 2018
Protocol Amendment 4, Version, 5.0:	04 March 2020

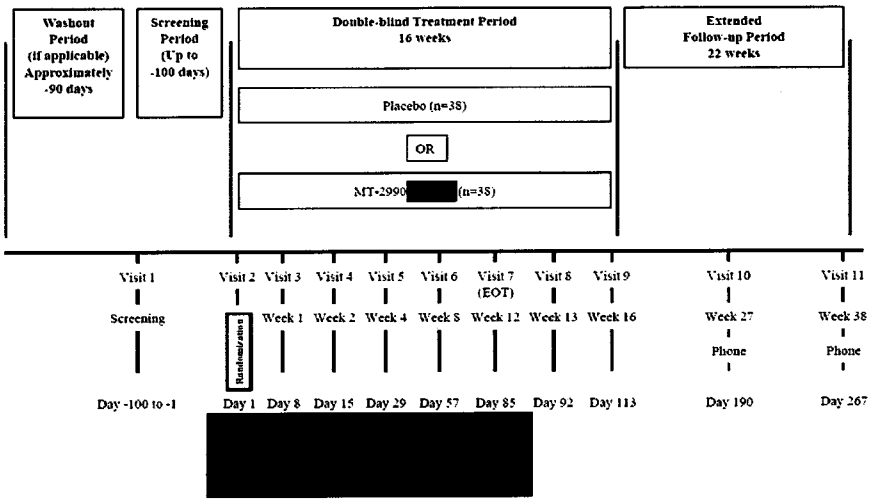
Strictly Confidential Information

1 SYNOPSIS

Name of Company **Mitsubishi Tanabe Pharma Development America, Inc.**	**Individual Study Table Referring to Module 5 of the CTD**	**(For National Authority Use Only)**
Name of Finished Product **MT-2990**	**Volume:**	
Name of Active Ingredient **MT-2990**	**Page:**	

Study Protocol	MT-2990-A01
Title of Study	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
Study Sites	Approximately 38 study sites are expected to participate in the United States (US)
Studied Period	Estimated date first subject enrolled: December 2018 (randomized) Estimated date last subject completed: February 2020
Development Phase	2
Objectives	**Primary Objective:** • To assess the efficacy of MT-2990 on nonmenstrual pelvic pain in women with endometriosis **Secondary Objectives:** • To assess the efficacy of MT-2990 on dysmenorrhea in women with endometriosis • To assess the effect of MT-2990 on dyspareunia • To assess the safety and tolerability of MT-2990 **Exploratory Objectives:** • To evaluate the impact of MT-2990 on resource utilization • To assess the impact of MT-2990 on endometriotic lesions • To evaluate human interleukin (IL)-33, IL-6, and IL-8 serum levels
Investigational Medicinal Product	MT-2990 is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds to human interleukin (IL)-33.
Treatment Regimen	MT-2990 [redacted] or placebo [redacted]

Name of Company **Mitsubishi Tanabe Pharma Development America, Inc.**	**Individual Study Table Referring to Module 5 of the CTD**	**(For National Authority Use Only)**
Name of Finished Product **MT-2990**	**Volume:**	
Name of Active Ingredient **MT-2990**	**Page:**	

Study Design Schematic	
Methodology	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. The approximate duration of the study per subject is 52 weeks, inclusive of the Screening period, Double-blind Treatment period, and the Extended Follow-up period. [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. [redacted] All efficacy and safety measures will be collected during the 16-week

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

Double-blind Treatment period. [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). [redacted]

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.

There will be 3 interim assessments for safety. 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.

Serious adverse events (SAE) will be collected from the time of signing the ICF. All adverse events (AEs) will be collected from Day 1 through the Double-blind Treatment period (Visit 9). All fractures will be collected as adverse events of special interest (AESI).

Blood and urine samples will be obtained at protocol prespecified time points for chemistry, hematology, [redacted] and pharmacokinetics (PK). Subjects will also be required to undergo transvaginal

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

	ultrasound (TVU) during Screening and at the Week 16 visit. The study does not require a laparoscopy procedure or dual-energy x-ray absorptiometry (DEXA) scan at any time during or after the study. All laparoscopic procedure data will be collected from the most recent laparoscopy procedure as well as any clinically indicated laparoscopy performed during the Double-blind Treatment period and Extended Follow-up period. If available, data will be collected from the most recent DEXA scan (within 1 year of Screening) and any DEXA scan conducted during the Double-blind Treatment period and Extended Follow-up period.
Assessments	**Safety Assessments:** • Physical examination (including breast examination) • Vital signs (blood pressure, pulse rate, and tympanic body temperature) • ECG parameters (including cardiac intervals: heart rate, PR, QRS, QT, QTcF, and QTcB) • Clinical laboratory assessments (hematology, biochemistry, coagulation, and urinalysis) • Treatment-emergent adverse events (TEAEs) **Biomarker Assessments:** [redacted] **Pharmacokinetic (PK) Assessments:** Blood samples will be collected at multiple study visits to measure PK parameters. Blood samples will be collected via cannulation or direct venipuncture in a suitable forearm vein. The actual date and time of each blood sample will be recorded in the subject's eCRF. **Immunogenicity Assessments:** Blood samples will be collected at multiple study visits to measure antibodies against MT-2990 in serum. Blood samples will be collected via cannulation or direct venipuncture in a suitable forearm vein. The actual date and time of each blood sample will be recorded in the subject's eCRF.
Number of Subjects	Approximately 76 subjects will be randomized into the study, with approximately 38 subjects in each treatment arm.

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

Diagnosis and Main Inclusion Criteria and Exclusion Criteria	**Inclusion Criteria:** 1. Subject must sign the written informed consent form (ICF) to participate in this study. [redacted] **Inclusion Criteria for Entry into the Washout Period (if applicable [in addition to Inclusion Criteria 5 through 9]):** 3. Subject agrees to approximately 90-day washout interval of hormonal therapies, if applicable. **Inclusion Criteria for Entry into the Screening Period:** 4. Subject undergoing the Washout period (if applicable), must have a menstrual cycle with an interval of 21 to 38 days prior to entering the Screening period. 5. Subject must have a body mass index < 45 kg/m^2 (inclusive) at Screening and Day 1. 6. Subject who has documented surgical/laparoscopy diagnosis of endometriosis within 10 years of the Screening period. [redacted] 8. Subject agrees to use 2 forms of nonhormonal contraception throughout the study (refer to Section 8.6.2). 9. In the Investigator's opinion, subject is able to understand the nature of the study and any risk involved in participation and is willing to cooperate and comply with the protocol restrictions and requirements including transvaginal ultrasound. [redacted] **Inclusion Criteria for Entry into the Double-blind Treatment Period:** 11. Subject must have had 2 menstrual cycles with an interval of 21 to 38 days prior to treatment Day1. [redacted]

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

[redacted]

Exclusion Criteria:

[redacted]

2. Subject is pregnant, breast feeding, or planning a pregnancy within the next 12 months.
3. Subject is < 6 months postpartum, postabortion, or postpregnancy at the time of entry into the Screening period.
4. Subject has a hormonal intrauterine device (IUD). If the hormonal IUD is removed prior to Screening and subject completes Washout period, subject will be eligible for study participation.

[redacted]

7. Subject with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2.0 × upper limit of normal (ULN) above the reference range any time prior to randomization.

[redacted]

9. Subject with immunosuppression due to underlying medical condition;
   a. Hereditary or congenital immunodeficiencies, cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia
   b. Current or anticipated use (within 6 months of randomization) of disease modifying doses of anti-rheumatic drugs (eg, azathioprine, cyclophosphamide, cyclosporine, methotrexate), or immunotherapy such as tumor necrosis factor (TNF)-α or interleukin (IL) inhibitors use within 12 weeks of the Screening visit.

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

c. History of solid organ or bone marrow transplantation.
d. Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥ 20 mg/day of prednisone equivalent within 12 weeks of the Screening visit.

[redacted]

13. Subject with QTcF or QTcB ≥ 450 msec or clinically important abnormal findings on the ECG during the Screening visit.
14. Subject is not up-to-date on breast screening according to current guidelines.

[redacted]

17. Subject has a surgical history of:
    a. hysterectomy (with or without oophorectomy);
    b. bilateral oophorectomy;
    c. any other recent major surgery (including laparotomy for endometriosis) within 6 months or any minor surgery (including laparoscopy for endometriosis) within 3 months prior to Treatment Day 1, or scheduled for a surgical procedure during the course of study.
18. Subject is required more than 2 weeks of continuous use of prohibited long-acting narcotic or immediate release narcotic for treatment of endometriosis-associated pain within 6 months of entry into the Washout period (if applicable) or Screening period.
19. Subject has chronic pelvic pain for nonendometriosis related causes (eg, interstitial cystitis, chronic pelvic inflammatory diseases, adenomyosis, fibroids, nonendometriosis-related pelvic adhesive disease, irritable bowel syndrome, and other nonendometriosis related causes), which require systemic pharmaceutical chronic therapy for pain.

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD Volume:	(For National Authority Use Only)
Name of Finished Product MT-2990		
Name of Active Ingredient MT-2990	Page:	

	20. Subject with other chronic pain syndrome (eg, fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headaches, and other chronic pain) which require chronic analgesic or other chronic therapy. [redacted] 22. Subject with a clinically significant gynecologic condition identified on the transvaginal ultrasound (TVU) during the Screening period such as: • Complex ovarian cyst > 3 cm or simple ovarian cyst > 5 cm that persists on repeat TVU; • Clinically significant endometrial pathology; • Single fibroid ≥ 4 cm or multiple (> 4) fibroids that measure ≥ 2 cm or symptomatic submucosal fibroid of any size. 23. Subject with a current history of undiagnosed abnormal genital bleeding. [redacted]
Data Monitoring Committee	An independent Data Monitoring Committee (DMC) will convene to review safety data when; a. 20 subjects are randomized and have completed the Week 2 visit b. 50% of subjects are randomized and have completed the Week 4 visit c. 50% of subjects are randomized and have completed the Week 16 visit
Endpoints	**Primary Efficacy Endpoint:** • Mean change from Baseline to Week 16 in nonmenstrual pelvic pain [redacted] **Key Secondary Efficacy Endpoints:** • Mean change from Baseline to Week 16 in dysmenorrhea [redacted] **Secondary Efficacy Endpoints:** • Mean change from Baseline to Week 16 in dyspareunia score [redacted] • Mean change from Baseline to Week 16 in nonmenstrual pelvic pain [redacted] • Mean change from Baseline to Week 16 in dysmenorrhea [redacted] • Mean change from Baseline to Week 16 in dyspareunia score [redacted] • [redacted] • Mean change from Baseline to Week 16 in pill count of any rescue analgesic use

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

- Mean change from Baseline to Week 16 in opioid pill count
- Time to rescue medications
- Percentage of nonmenstrual pelvic pain responders at Week 16 [redacted]
- Percentage of dysmenorrhea responders at Week 16 [redacted]
- Mean percentage change from Baseline to each month in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline to each month in dysmenorrhea [redacted]
- Percentage of nonmenstrual pelvic pain responders at Week 16 [redacted]
- Percentage of dysmenorrhea responders at Week 16 [redacted]
- Mean percentage change from Baseline to each month in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline to each month in dysmenorrhea [redacted]
- Number and percentage of women who responded [redacted]
- Mean change from Baseline to Weeks 4, 8, 12, and 16 on each dimension of [redacted]
- Number and percentage of women who responded [redacted]

Safety Endpoints:

- 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)
- TEAEs

Exploratory Endpoints:

[redacted]

Name of Company **Mitsubishi Tanabe Pharma Development America, Inc.**	**Individual Study Table Referring to Module 5 of the CTD** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Finished Product **MT-2990**		
Name of Active Ingredient **MT-2990**		

	[redacted]
Statistical Methods	The statistical analysis will be performed using SAS® version 9.2 or higher. The ITT population will be used for all clinical efficacy analyses; the PP population will also be used for the primary and secondary efficacy endpoints for confirming robustness. The Safety population will be used for all safety summaries. PK assessments will be performed using the PK population. All formal statistical tests will be done at the 5% 2-sided significance level. Point estimates will have 2-sided 95% confidence intervals (CIs) where applicable. Where appropriate, variables will be summarized descriptively (frequency and percentage 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 arm. Statistical summaries will be presented for the changes from Baseline to each time point in efficacy endpoints where applicable. **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 to 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 SD of 0.65, based on results from the effect of [redacted] As this study is an 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

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

in this study.

Analysis Populations:

- Randomized population will include all randomized subjects.
- Safety 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 1 postscreening 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.
- PK population will include all randomized subjects who received at least 1 dose of MT-2990 and have at least 1 postdose value for plasma concentration without important protocol deviations which may affect the PK of MT-2990.

Primary Analysis:

Change from Baseline to Weeks 4, 8, 12, and 16 in the monthly 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 as a covariate; weeks and treatment as fixed effect; subjects as random effect. Point estimates and 95% CIs for the difference between each active dose and placebo at Week 16 and other time points will be obtained.

Secondary Analysis:

Similar analysis to the primary analysis will be conducted for the primary endpoint using the last observation carried forward method for the missing value at or before the Week 16 visit.

Similar analysis to the primary endpoint will be conducted to the key secondary endpoint.

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

Time to rescue medications will be analyzed using a log-rank test and significance difference test based on Restricted Mean Survival Time.

Fisher's exact test will be used to test the statistical significance between MT-2990 and placebo for the number of women who responded "much improved" or "very much improved" on the PGIC, and "Extremely Satisfied" or "Satisfied" on the ETSQ.

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

[redacted]

Exploratory Analysis:

Exploratory analysis may be performed. Details about exploratory analysis will be specified in the Statistical Analysis Plan (SAP).

Safety Evaluation:

AEs are considered as treatment-emergent if they occur after administration of the first dose of study medication or if a predose 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 arm 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. All fractures will be collected as an AESI.

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

Other safety measures (eg, bone fractures, DEXA scan, antibodies to MT-2990) will be summarized according to the data type.

Physical examination data will be listed by subject. Changes in physical examinations will be described in the text of the Clinical Study Report (CSR).

Pharmacokinetic Evaluation:

Name of Company Mitsubishi Tanabe Pharma Development America, Inc.	Individual Study Table Referring to Module 5 of the CTD	(For National Authority Use Only)
Name of Finished Product MT-2990	Volume:	
Name of Active Ingredient MT-2990	Page:	

All PK data will be listed and summarized using the number of observations, mean, SD, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. Pharmacokinetic (PK) concentrations will be summarized by treatment and planned sampling time.

Population PK analysis will be performed using the plasma concentration of MT-2990 obtained in this study in combination with data obtained from other clinical studies. Population PK analysis results will be reported separately from the CSR. Details of the population PK analysis will be presented in a modelling plan.

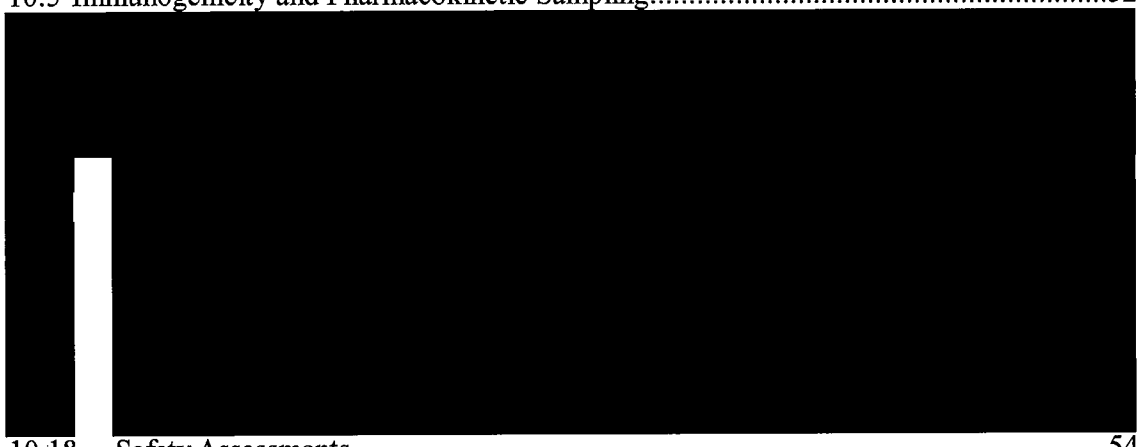
Immunogenicity Evaluation:

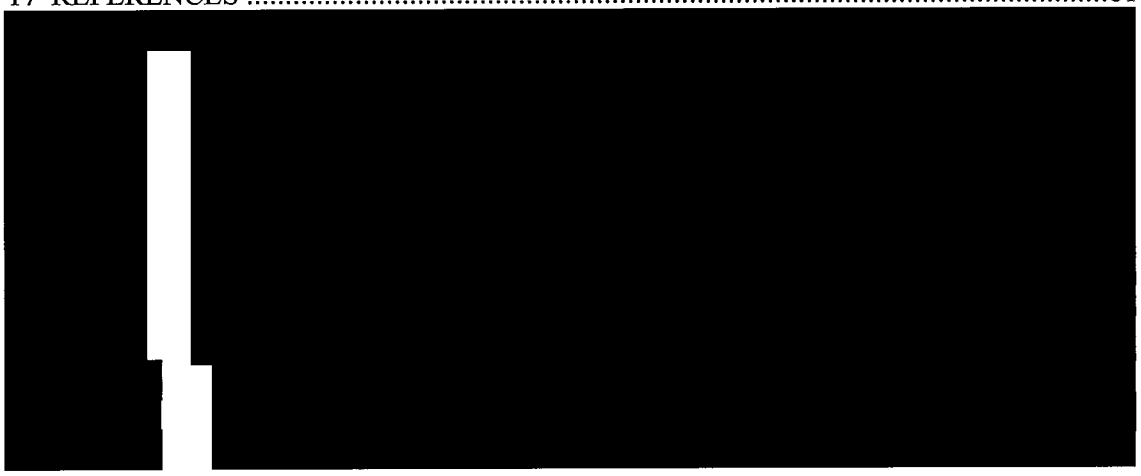
The proportion of subjects who develop antibodies against MT-2990 in serum will be summarized using descriptive statistics on the Safety Population. Further details will be provided in the SAP.

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.

TABLE OF CONTENTS





LIST OF TABLES

LIST OF FIGURES

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransferase
AUC	area under the serum concentration-time curve
$AUC_{0-\infty}$	area under the serum concentration-time curve extrapolated from time zero to infinity
$AUC_{0\text{-last}}$	area under the serum concentration-time curve from time zero to the last measurable concentration
[redacted]	[redacted]
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval(s)
C_{max}	maximum serum concentration
[redacted]	[redacted]
CS	clinically significant
CSR	Clinical Study Report
CV%	coefficient of variation percentage
DEXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
e-Diary	electronic-Diary
[redacted]	[redacted]
EMEA	European Medicines Agency
EOS	End of Study
EOT	End-of-treatment
[redacted]	[redacted]
ET	early termination
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	heart rate
[redacted]	[redacted]
IB	Investigator's Brochure
IC90	90% inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN	interferon
IgG1	Immunoglobulin G1
IL	interleukin

Abbreviation	Definition
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IWRS	Interactive Web-based Response System
[redacted]	[redacted]
N	number of subjects
n	number of observations
NAB	neutralizing antibody
NCS	not clinically significant
[redacted]	[redacted]
NSAID	nonsteroidal anti-inflammatory drug
[redacted]	[redacted]
PK	pharmacokinetic(s)
PP	per-protocol
PRO	Patient Reported Outcomes
[redacted]	[redacted]
PTE	pretreatment event
QTcF	Corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
[redacted]	[redacted]
ST2	growth stimulation expressed gene 2
ST2L	trans-membrane form ST2
sST2	soluble form ST2
SUSAR	Suspected Unexpected Serious Adverse Reaction
t½	apparent elimination half-life in serum
TEAE	treatment-emergent adverse events
TMF	Trial Master File
TVU	transvaginal ultrasound
ULN	upper limit of normal
Vss	apparent volume of distribution at steady state
WMA	World Medical Association

3 SIGNATURES

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

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

Sponsor Signatory:

[redacted]

Date

[redacted]

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

SPONSOR'S RESPONSIBLE SIGNATORY

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

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

Sponsor Signatory:

[redacted]

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

STATISTICIAN

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

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

Statistician:

[redacted]

Date

[redacted]

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

PRINCIPAL INVESTIGATOR

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

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: _____

4 PROCEDURES IN CASE OF EMERGENCY

Table 1 Emergency Contact Information

Role in Study	Name	Address and Telephone Number
Clinical Study Leader	[redacted]	Mitsubishi Tanabe Pharma Development America, Inc. 525 Washington Boulevard, Suite 400 Jersey City, New Jersey 07310 [redacted] (m)
Responsible Physician Medical Monitor	[redacted]	[redacted]

5 INTRODUCTION

MT-2990 is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds to human interleukin (IL)-33.

IL-33 is an alarmin that acts upon both the innate and adaptive immune system and plays functional roles in both infectious and chronic inflammatory diseases.[1] This cytokine belongs to the IL-1 family. IL-33 is broadly expressed in many tissues but with restricted cell type expression in endothelial cells and epithelial cells. IL-33 is considered to be released from these cells after cell damage induced by allergens, viruses, and mechanical stress.[2,3] Growth stimulation expressed gene 2 (ST2) is a receptor of IL-33 and has at least 2 isoforms including a trans-membrane form ST2 (ST2L) and soluble form ST2 (sST2). ST2L is expressed on the cell surface of various immune cells including macrophages, T-helper 2 cells, mast cells, and group 2 innate lymphoid cells. IL-33 binds a heterodimeric receptor complex consisting of ST2L and IL-1 receptor accessory protein. This IL-33/ST2L signal transduction induces the secretion of numerous pro-inflammatory cytokines and chemokines. Soluble form ST2s (sT2) acts as a decoy receptor for IL-33 and thus inhibits the IL-33/ST2L signal transduction.[4, 5]

Women with endometriosis exhibit heightened local and systemic inflammation,[6] and it has been hypothesized that women who develop endometriosis have genetic, biochemical, or immune system dysfunction that does not allow the removal of the debris but rather facilitates menstrual tissue adhesion to peritoneal structures and endometriotic lesion formation.[7,8] In women with endometriosis, serum, peritoneal fluid, and/or tissue levels of IL-33 have been observed to be significantly higher in patients with advanced endometriosis and/or a deep infiltrating endometriosis compared to controls.[9,10,11] Administration of mouse recombinant IL-33 induces local and systemic inflammation and increased lesion size and vascularization in a syngeneic mouse model of endometriosis.[11] Therefore, it has been hypothesized that pharmacological blockade of IL-33 with MT-2990 in patients with endometriosis may reduce implant invasiveness, inflammatory pain, as well as possibly reduce in fibrosis associated with endometriotic lesions.

5.1 Nonclinical Pharmacology

5.2 Nonclinical Safety Pharmacology

[redacted]

5.3 Nonclinical Pharmacokinetics

[redacted]

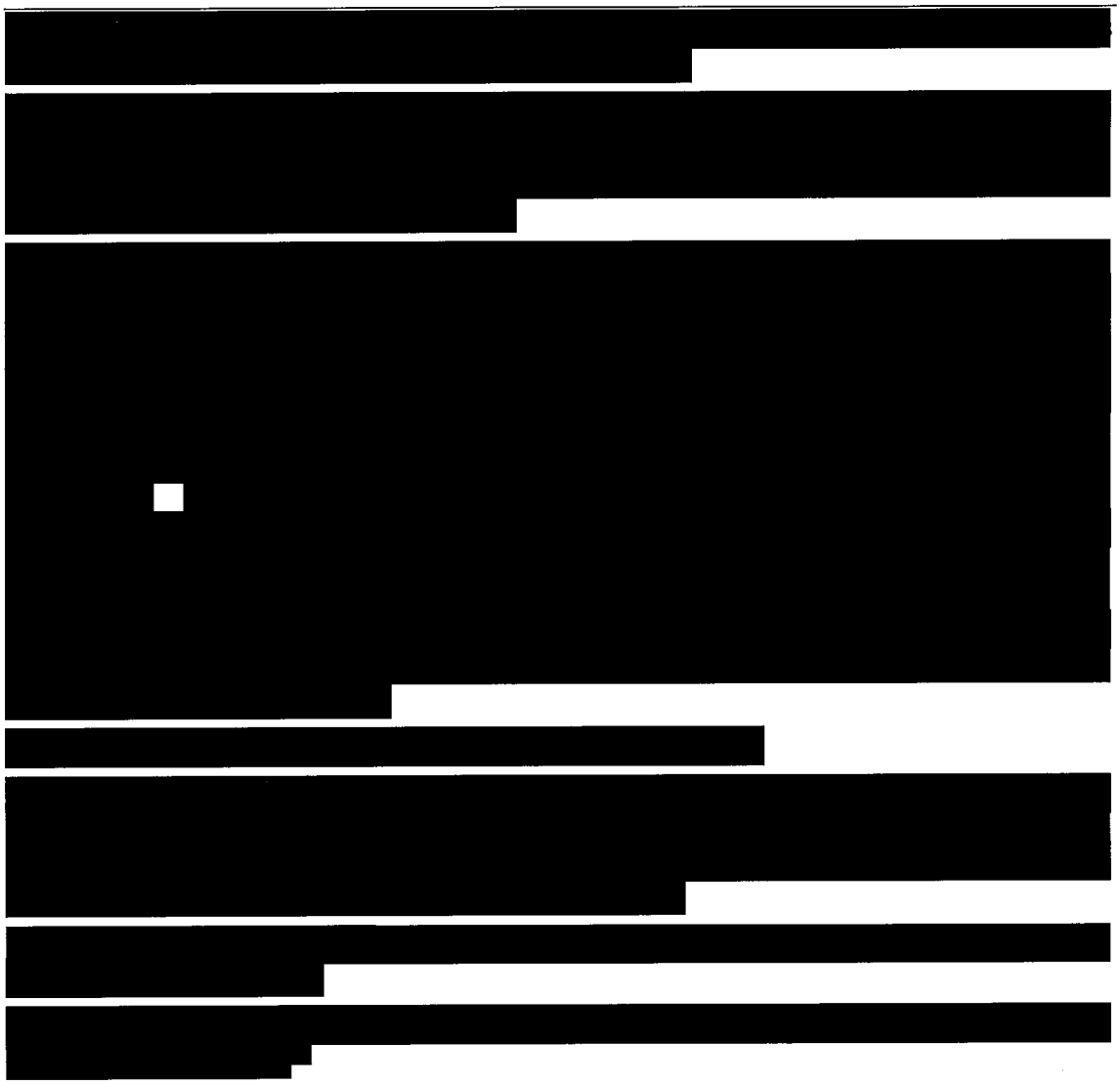
5.4 Nonclinical Toxicology

[redacted]

5.5 Clinical Studies

5.5.1 Study MT-2990-E01

[redacted]



6 OBJECTIVES 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. [redacted]

6.1 Study Objectives

6.1.1 Primary Objective

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

6.1.2 Secondary Objectives

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

6.1.3 Exploratory Objectives

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

6.2 Study Endpoints

6.2.1 Primary Endpoint

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

6.2.2 Key Secondary Efficacy Endpoints

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

6.2.3 Secondary Efficacy Endpoints

- Mean change from Baseline to Week 16 in dyspareunia score [redacted]
- Mean change from Baseline to Week 16 in nonmenstrual pelvic pain [redacted]
- Mean change from Baseline to Week 16 in dysmenorrhea [redacted]
- Mean change from Baseline to Week 16 in dyspareunia score [redacted]

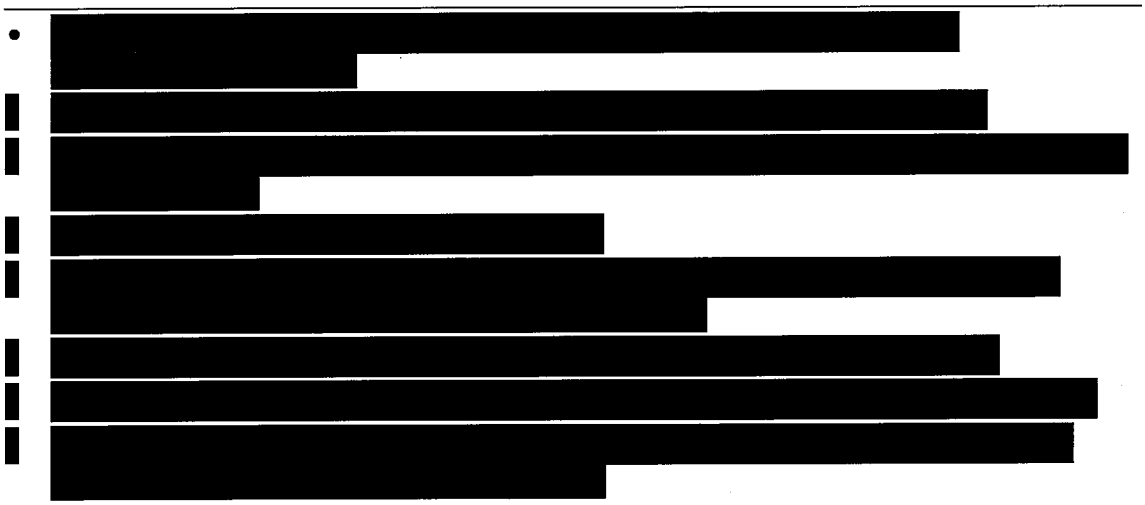
- [redacted]
- Mean change from Baseline to Week 16 in pill count of any rescue analgesic use
- Mean change from Baseline to Week 16 in opioid pill count
- Time to rescue medications
- Percentage of nonmenstrual pelvic pain responders at Week 16 [redacted]
- Percentage of dysmenorrhea responders at Week 16 [redacted]
- Mean percentage change from Baseline to each month in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline to each month in dysmenorrhea [redacted]
- Percentage of nonmenstrual pelvic pain responders at Week 16 [redacted]
- Percentage of dysmenorrhea responders at Week 16 [redacted]
- Mean percentage change from Baseline to each month in nonmenstrual pelvic pain [redacted]
- Mean percentage change from Baseline to each month in dysmenorrhea [redacted]
- Number and percentage of women who responded [redacted]
- Mean change from Baseline to Weeks 4, 8, 12, and 16 on each dimension of [redacted]
- Number and percentage of women who responded [redacted]

6.2.4 Safety Endpoints

- Physical examination (including breast examination)
- Vital signs (blood pressure, pulse rate, and tympanic body temperature)
- ECG parameters (including cardiac intervals: heart rate, PR, QRS, QT, QTcF and QTcB)
- Clinical laboratory assessments (hematology, biochemistry, coagulation, and urinalysis)
- TEAEs

6.2.5 Exploratory Endpoints

- [redacted]



7 STUDY DESIGN

7.1 Overall Study Design

7.1.1 Study Methodology

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. Approximately 76 subjects will be randomized into the study, with approximately 38 subjects in each treatment arm. The approximate duration of the study per subject is 52 weeks, inclusive of the Screening period, Double-blind Treatment period, and the Extended Follow-up period.

[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 in a ratio of 1:1. [redacted]

All efficacy and safety measures will be collected during the 16-week Double-blind Treatment period. [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). [redacted]

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: at 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.

There will be 3 interim assessments for safety. 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.

Serious adverse events (SAE) will be collected from the time of signing the ICF. All adverse events (AEs) will be collected from Day 1 through the Double-blind Treatment period (Visit 9). All fractures will be collected as events of special interest (AESI).

Blood and urine samples will be obtained at protocol prespecified time points for chemistry, hematology, [redacted] and PK. Subjects will be required to undergo TVU during Screening and at the Week 16 visit.

The study does not require a laparoscopy procedure or dual-energy x-ray absorptiometry (DEXA) scan at any time during or after the study. All laparoscopic procedure data will be collected from the most recent laparoscopy procedure as well as any clinically indicated laparoscopy performed during the Double-blind Treatment period and Extended Follow-up period.

If available, data will be collected from the most recent DEXA scan (within 1 year of Screening) and any DEXA scan conducted during the Double-blind Treatment period and Extended Follow-up period.

The study design is presented in Figure 1.

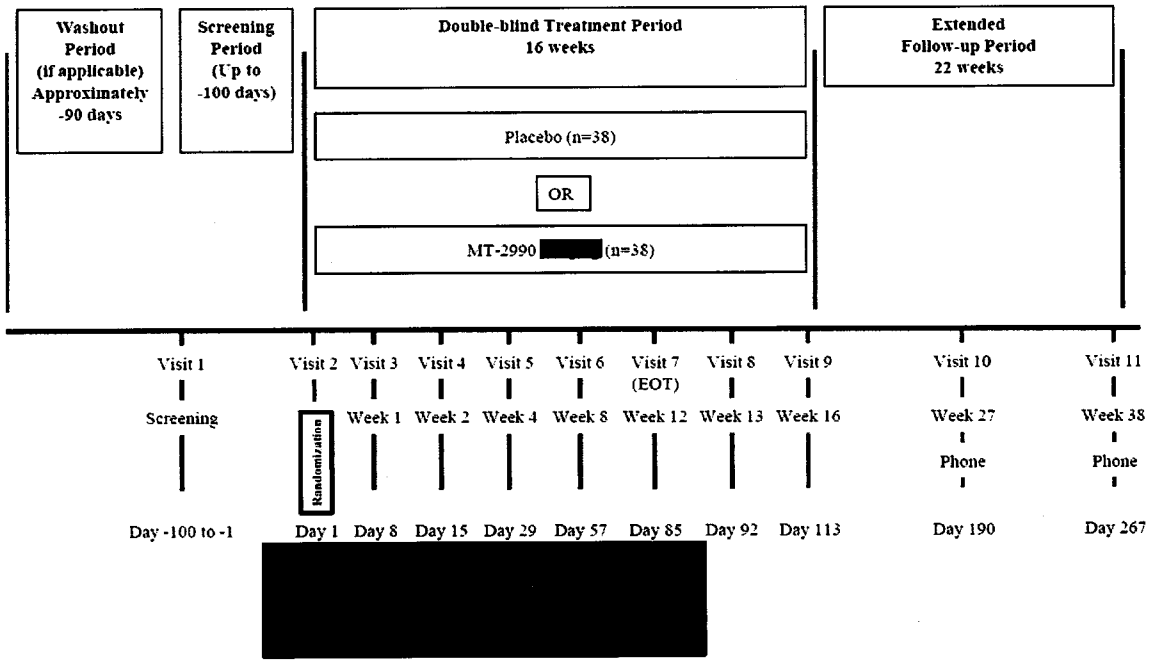


Figure 1 Study Design Schematic

7.2 Rationale for Study Design and Treatment Regimens

The objectives of this study are to obtain efficacy, safety, and tolerability data for MT-2990 when administered as multiple doses in women with endometriosis experiencing endometriosis related pain.

Women with laparoscopically diagnosed endometriosis with moderate or severe endometriosis-associated pain will be enrolled into the study. Moderate-severe pain subset is an appropriate target, as these patients will likely have been laparoscopically diagnosed and progressed through first line therapies (e [redacted]

In an attempt to assess the baseline pain scores, at least 2 menstrual cycles with an interval of 21 to 38 days documented within the Screening period up to 100 days will be required. [redacted]

Primary and secondary endpoints are subject centric and will evaluate the pain associated with endometriosis. Nonmenstrual pelvic pain is to be evaluated as the primary endpoint and dysmenorrhea will be evaluated as the key secondary endpoint. Although there are no established guidelines for endometriosis related pain, American Society for Reproductive Medicine recommends the daily rating of pelvic pain and daily rating of dysmenorrhea as primary outcome measures.[19]Subjects will use the electronic (e)-Diary to report daily assessments of nonmenstrual pelvic pain and dysmenorrhea [redacted]

Pharmacokinetic data from this study will be used in combination with other clinical studies for population PK analysis.

7.2.1 Risk:Benefit Statement

Treatment of moderate to severe pain related to endometriosis is a significant unmet need. Young women at childbearing age develop endometriosis related pain and other complications which effects their productivity at peak age.

The current study will evaluate the effect of MT-2990 on treatment of moderate to severe endometriosis related pain. This study will evaluate if MT-2990 may treat the endometriosis related pain.

MT-2990 is a human IgG1 monoclonal antibody that highly and specifically binds to IL-33 among IL-1 family molecules. It is under investigation for the potential clinical benefits for the treatment of moderate to severe endometriosis-related pain in women with surgically diagnosed endometriosis.

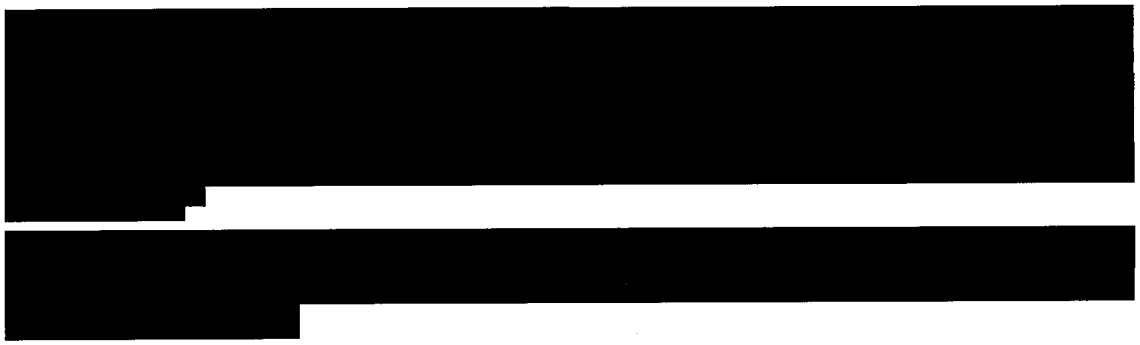
The overall nonclinical safety data and profile is supportive of the clinical use of MT-2990 in human clinical trials. Nonclinical studies have demonstrated no significant toxicity of MT-2990.

In the 1 clinical study conducted to date, single doses of MT-2990 [redacted] were considered to be safe and well tolerated in healthy male subjects. No deaths, SAEs, AEs leading to withdrawal, or severe TEAEs occurred during the study.

The Sponsor will undertake all reasonable measures, to minimize the risk to subjects. Subjects will receive no further dosing if they meet any of the withdrawal criteria listed in Section 8.5.

This study will provide additional efficacy and safety information on the risk:benefit profile of MT-2990.

7.2.2 Rationale for Dose Selection



8 SELECTION AND WITHDRAWAL OF SUBJECTS

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

8.1 Number of Subjects

Approximately 76 subjects will be randomized into the study, with approximately 38 subjects in each treatment arm.

8.2 Recruitment Methods

Subjects will be recruited via a variety of methods including, but not limited to, site review of subject records, media advertising, Contract Research Organization, and recruitment vendors, if appropriate. All recruitment material will be approved by Institutional Review Board (IRB) prior to implementation.

A sufficient number of subjects will be screened to ensure that the planned sample size is achieved. Only subjects who are eligible for the study will be enrolled.

8.3 Subject Inclusion Criteria

1. Subject must sign the written informed consent form (ICF) to participate in this study.

[redacted]

Inclusion Criteria for Entry into the Washout Period (if applicable [in addition to Inclusion Criteria 5 through 9]):

3. Subject agree to approximately 90-day washout interval of hormonal therapies, if applicable.

Inclusion Criteria for Entry into the Screening Period

4. Subject undergoing the Washout period (if applicable), must have a menstrual cycle with an interval of 21 to 38 days prior to entering the Screening period.

5. Subject must have a body mass index < 45 kg/m^2 (inclusive) at Screening and Day 1.

6. Subject who has documented surgical/laparoscopy diagnosis of endometriosis within 10 years of the Screening period.

[redacted]

8. Subject agrees to use 2 forms of nonhormonal contraception throughout the study (refer to Section 8.6.2).

9. In the Investigator's opinion, subject is able to understand the nature of the study and any risk involved in participation and is willing to cooperate and comply with the protocol restrictions and requirements including TVU.

[redacted]

Inclusion Criteria for entry into the Double-blind Treatment Period

11. Subject must have had 2 menstrual cycles with an interval of 21 to 38 days prior to treatment Day1.

[redacted]

8.4 Subject Exclusion Criteria

[redacted]

2. Subject is pregnant, breast feeding, or planning a pregnancy within the next 12 months.

3. Subject is < 6 months postpartum, postabortion, or postpregnancy at the time of entry into the Screening period.

4. Subject has a hormonal intrauterine device (IUD). If the hormonal IUD is removed prior to Screening and subject completes Washout period, subject will be eligible for study participation.

[redacted]

[redacted]

7. Subject with aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin ≥2.0 × upper limit of normal (ULN) above the reference range any time prior to randomization.

[redacted]

9. Subject with immunosuppression due to underlying medical condition;
    a. Hereditary or congenital immunodeficiencies, cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia
    b. Current or anticipated use (within 6 months of randomization) of disease modifying doses of anti-rheumatic drugs (eg, azathioprine, cyclophosphamide, cyclosporine, methotrexate), or immunotherapy such as tumor necrosis factor (TNF)-α or interleukin (IL) inhibitors use within 12 weeks of the Screening visit.
    c. History of solid organ or bone marrow transplantation.
    d. Long term use (≥ 7 days) of oral or parenteral glucocorticoids at a dose of ≥ 20 mg/day of prednisone equivalent within 12 weeks of the Screening visit.

[redacted]

13. Subject with QTcF or QTcB ≥ 450 msec or clinically important abnormal findings on the ECG during the Screening visit.

14. Subject is not up-to-date on breast screening according to current guidelines.

[redacted]

17. Subject has a surgical history of:

    a. hysterectomy (with or without oophorectomy);
    b. bilateral oophorectomy;
    c. any other recent major surgery (including laparotomy for endometriosis) within 6 months or any minor surgery (including laparoscopy for endometriosis) within 3 months prior to Treatment Day 1, or scheduled for a surgical procedure during the course of study.

18. Subject is require more than 2 weeks of continuous use of prohibited long-acting narcotic or immediate release narcotic for treatment of endometriosis-associated pain within 6 months of entry into the Washout period (if applicable) or Screening period.

19. Subject has chronic pelvic pain for nonendometriosis related causes (eg, interstitial cystitis, chronic pelvic inflammatory diseases, adenomyosis, fibroids, nonendometriosis-related pelvic adhesive disease, irritable bowel syndrome, and other nonendometriosis related causes), which require systemic pharmaceutical chronic therapy for pain.

20. Subject with other chronic pain syndrome (eg, fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headaches, and other chronic pain) which requires chronic analgesic or other chronic therapy.

[redacted]

22. Subject with a clinically significant gynecologic condition identified on the TVU during the Screening period such as:

    - Complex ovarian cyst > 3 cm or simple ovarian cyst > 5 cm that persists on repeat TVU;
    - Clinically significant endometrial pathology;
    - Single fibroid ≥ 4 cm or multiple (> 4) fibroids that measure ≥ 2 cm or symptomatic submucosal fibroid of any size.

23. Subject with a current history of undiagnosed abnormal genital bleeding.

[redacted]

8.5 Withdrawal of Individual Subjects

A subject will be withdrawn if ANY of the following criteria are met:

- The subject wishes to withdraw from further participation
- The subject is significantly noncompliant with the Protocol
- Continuing in the study would be detrimental to the subject's safety in the opinion of the Investigator, eg, the subject experiences a pretreatment event (PTE) or an AE that requires early termination (ET) because continued participation poses an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE or AE
- Subjects who become pregnant during the study should be withdrawn from study treatment. Refer to Section 12.9 for necessary documentation and procedures for following up with the subject
- Subjects who develop:
  - Hypersensitivity reactions, such as anaphylaxis and moderate to severe infusion-related reactions.
  - Abnormal hematologic indices as below:
    - White blood cell count (WBC) < 3000/mm3 (< 3.0×10^9/L) or absolute neutrophil count < 1,500/μL
    - Platelets < 100,000/μL
    - Hemoglobin < 8 g/dL

Note: If a subject has a decline of hemoglobin to < 9 g/dL, hemoglobin will be repeated within 2 weeks.

- ALT or AST > 5 times ULN
- ALT or AST > 3 times ULN sustained for more than two weeks
- ALT or AST > 3 times ULN AND total bilirubin > 2 X ULN or international normalized ratio > 1.5

Note: If a subject experiences elevated ALT or AST ≥ 3 times ULN, liver tests (ALT, AST, bilirubin, ALP, gamma-glutamyl transferase, and creatinine kinase) will be repeated within 3 to 5 days.

In addition, a subject may be withdrawn at any time for reason(s) other than those listed here. Medical monitor should be notified for all withdrawals.

If a subject is withdrawn prematurely from the study, the date the subject is withdrawn from the study and the reason for withdrawal will be recorded in the electronic Case Report Form (eCRF).

In case of withdrawal of a subject, the ET assessments should be performed per Table 2.

Reporting events as a SAE must be considered in cases where the AE has led to a withdrawal or the withdrawal is for a safety reason and, therefore, may be medically important, in

accordance with Section 12.

Any unresolved AE or SAE will be followed up according to Section 12.10.

In the event that a subject elects not to return to the clinical site for the ET 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 ET assessments.

Subjects who are withdrawn from the study following randomization may not re–enter the study.

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

8.6 Lifestyle Restrictions

Subjects will be advised to adhere to the restrictions detailed in the following subsections.

8.6.1 Alcohol Restrictions

Subjects are prohibited from excessive consumption of food or drink containing alcohol. Over the course of the study, subjects should not exceed 8 grams (equates to approximately 1 drink [1 glass of wine; one 12-ounce beer; 1 mixed drink/cocktail]) of alcohol per day.

8.6.2 Contraception

Subjects must agree to use 2 forms of nonhormonal dual contraception consistently throughout the study and until 3 months after the last dose of study drug. After Week 16 (Visit 9), if preferable, the subject may begin the use of hormonal contraception in place of nonhormonal dual contraception. Subjects must have negative urine pregnancy tests during the Screening period and a negative urine pregnancy test prior to the first dose of study medication on Day 1. Acceptable methods of dual contraception include the following combinations:

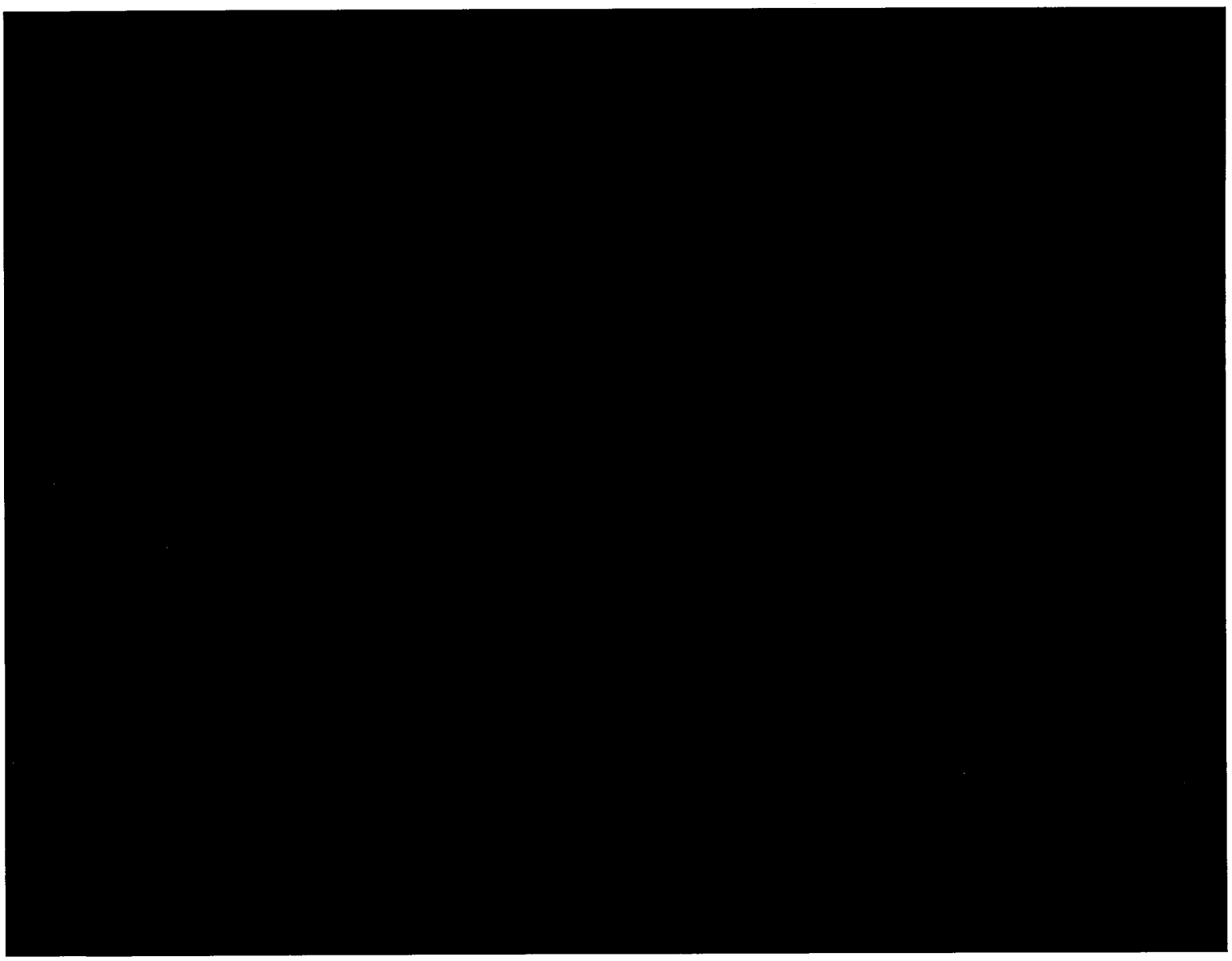
- Condoms used with spermicide (cream, spray, foam, gel, suppository, or polymer film);
- Diaphragm used with spermicide (condom may or may not be used);
- Cervical cap used with spermicide (condom may or may not be used);
- Vaginal sponge impregnated with spermicide used with a condom.

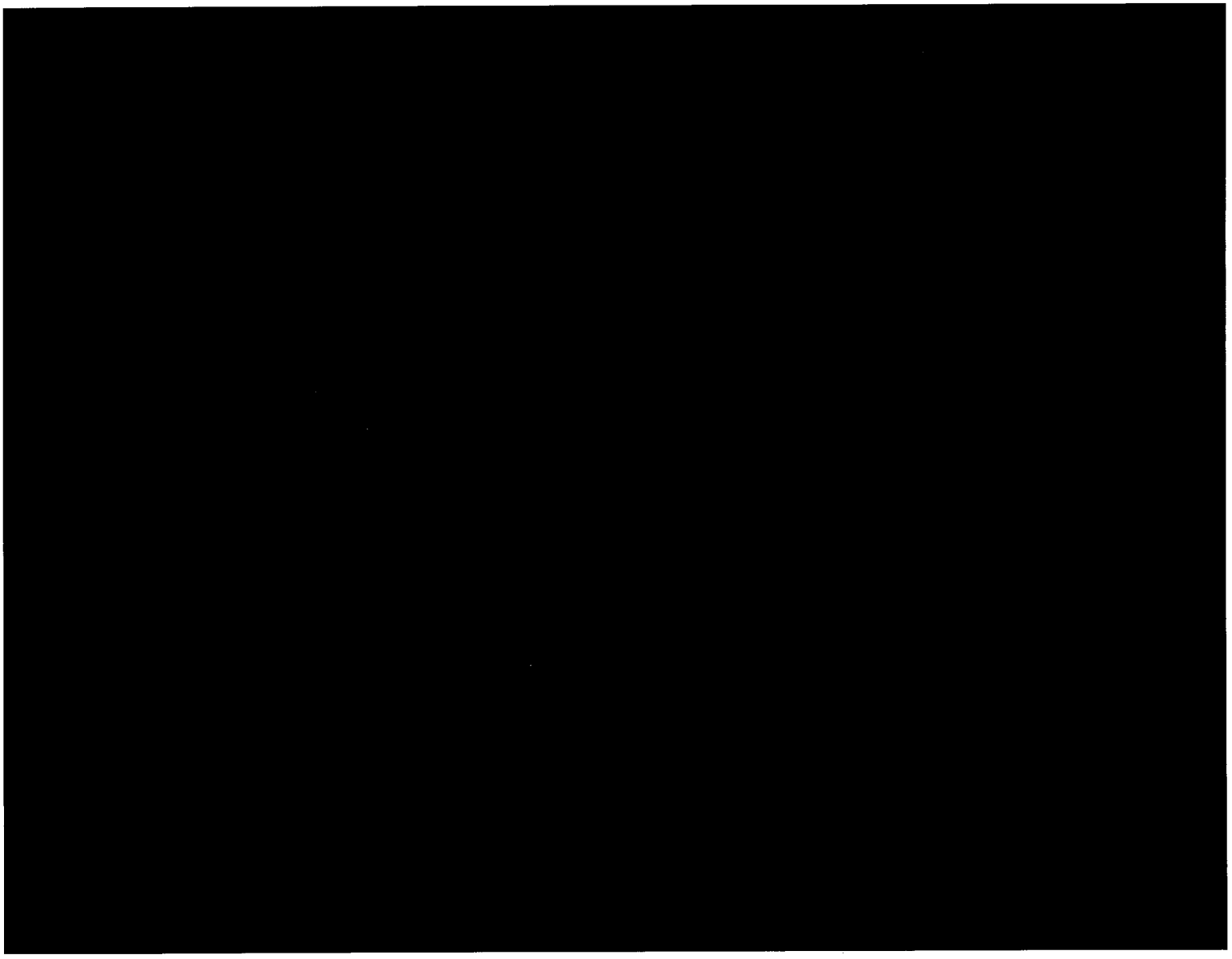
Subject is not required to use dual contraception methods if:

- Sexual partner(s) has undergone male sterilization (eg, vasectomy, at least 6 months prior to Screening or with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate, bilateral orchiectomy);
- Subject has had a bilateral tubal occlusion (including ligation and blockage methods such as Essure®), at least 3 months prior to Screening;
- Subject is not sexually active with men; periodic sexual relationship(s) with men requires

the use of nonhormonal contraception as indicated above;

- Hormonal contraception is started 3 months after the last dose of study drug.





9.1 Description of Study Periods

Refer to Table 2 for an outline of procedures required at each study period and/or visit.

Prior to performing any study procedures, the Investigator (or designated personnel) will ensure that the subject is given full and adequate oral and written information about the study and the subject must sign the ICF, as described in Section 15.2.1.

9.1.1 Screening Period

[redacted]Screening assessments will be performed from Day -100 to Day -1. Subjects will be requested to attend the clinic after a 10-hour fasting period (except for water intake). All Screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

Subject must have:

- at least 2 menstrual cycles with an interval of 21 to 38 days prior to treatment Day 1
- [redacted]

A TVU may be scheduled and performed at any time during the Screening period (refer to Section 10.18.4 for further details).

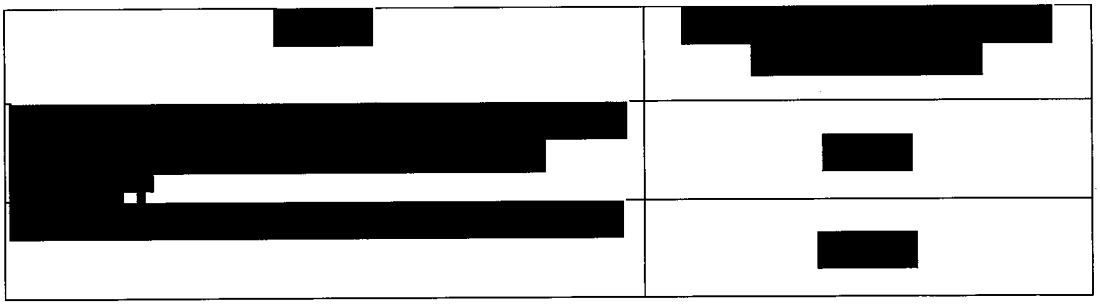
9.1.1.1 Washout Period (if applicable)

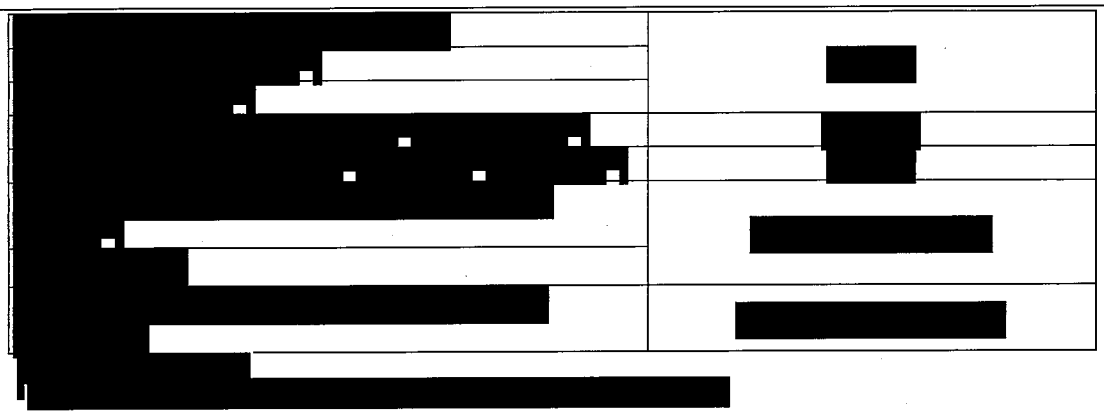
If applicable, subjects will complete a Washout period (approximatly 90 days) of hormonal therapies and must have a mentrual cycle with an interval of 21 to 38 days prior to entering the Screening period. For further details or any questions to assess the eligibility for the Screening period, please call the medical monitor.

Subjects who have received any of the following will require a Washout period as described in the Table 3.

Non-hormonal IUD is not required to be removed if a patient has had no adverse reactions (eg, anemia, backache, dysmenorrhea, dyspareunia, expulsion [complete or partial], prolonged menstrual flow, menstrual spotting, pain and cramping, and vaginitis) due to the non-hormonal IUD for more than 3 months before study participation.

[redacted]





9.1.2 Re-screening

If a subject has not met all eligibility criteria at the end of the Screening period, the subject will be registered as a screen fail. Screen fail subjects may be eligible for re-screening one time. If subject is screen failed due to laboratory measures only, a total 2 re-screenings > 2 weeks apart can be performed. For technical errors, please contact medical monitor.

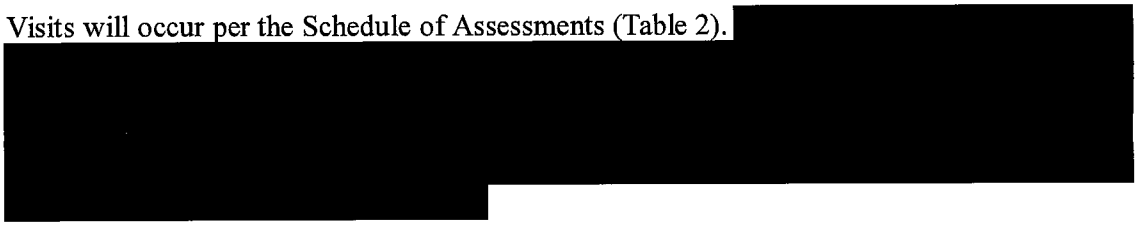
Rescreened subjects must first be registered as screen failures and subsequently registered as rescreens. Once the subject is registered as rescreened, a new Screening window will begin. The rescreened subject will be assigned a new unique Subject Identifier and the previous Subject Identifier will be noted. If the re-screening period begins more than 30 days after the original signing of the ICF, all Screening procedures, including ICF, must be repeated.

9.1.3 Double-Blind Treatment Period

Subjects who successfully complete the Screening period will return to the study clinic on Day 1 and inclusion and exclusion criteria will be reviewed to confirm eligibility. Subjects will be requested to attend the clinic after a 10hour fasting period (except for water intake).

ligible subjects will then be randomized and dosing will begin on Day 1 (Visit 2).

Visits will occur per the Schedule of Assessments (Table 2).



Site staff will monitor e-Diary compliance and contact subjects to rectify, if noncompliant. Subjects and sites will be auto-notified by e-Diary vendor if the subject is noncompliant

(eg, missed/erroneous data entry).

9.1.4 Extended Follow-up Period

Extension visits will be conducted via a telephone call at Week 27 (Visit 10) within ± 14 days and at Week 38 (Visit 11) within ± 14 days. [redacted]

9.1.5 Early Termination

For all subjects, Visit 9 ([ET], Week 16) assessments should be performed, per the Schedule of Assessments (Table 2).

Any unresolved AE or SAE will be followed up according to Section 12.

In the event that a subject elects not to return to the clinical site for the ET 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.

9.1.6 Unscheduled Visits

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

Additional unscheduled safety assessments such as routine blood sampling 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.

9.1.7 Poststudy Access to Treatment

MT-2990 will not be available to subjects following study termination or completion of the study in accordance with study information that has been provided to the subject.

10 STUDY PROCEDURES

10.1 Informed Consent Form

The Investigator or designee will fully explain the nature of the study to subjects using the IRB-approved ICF. When the subject agrees to participate in the study, the subject must voluntarily sign an ICF prior to the initiation of any study procedures. A copy of the signed and dated ICF will be given to the subject. The signed and dated original ICF will be retained by the Investigator. Informed consent will be obtained from all subjects. A subject cannot be entered into the study until she has signed and dated the ICF. 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 her participation in the study. Refer to Section 15.2.1 for further details.

10.2 Demographics

Demographics will include date of birth, sex, weight, height, ethnicity, and race.

10.3 Medical History

Medical history will include any significant, relevant past conditions, and any current medical conditions including drug use, smoking, alcohol, or surgeries.

10.4 Prior and Concomitant Medications

At the Washout and Screening Periods, subjects will be asked what medications they have taken during the last 3 months and all medications will be recorded as prior medications in the subject's source documents.

Concomitant medication is defined as any medication, other than the study medication, which is taken during the study from the Washout and Screening Periods to the EOS Visit, including prescription, herbal and over-the-counter medications. All concomitant medications taken while the subject is participating in the study will be recorded in the eCRF.

[redacted]

10.4.1 Permitted Medication

Medicines, which, in the opinion of the Sponsor and Investigator, will not interfere with the study procedures or compromise safety may be used (eg, occasional use of acetaminophen for

mild analgesia). However, any other concomitant medication will be given only if deemed necessary by the Investigator or the subject's personal physician.

10.4.2 Prohibited Medication

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

Subjects must not take any prescribed or nonprescribed systemic or topical medication (including herbal remedies) unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study procedures or compromise safety.

Subjects must not take hormonal contraceptives.

10.5 Immunogenicity and Pharmacokinetic Sampling

The timings of blood sampling to measure anti-MT-2990 antibody and PK assessments are presented in Table 2 but may be subject to change based on the ongoing review of data.

Additional blood samples may be taken from each subject; however, the maximum volume of blood withdrawn per subject will not exceed the limit detailed in Section10.18.6. Any changes to the scheduled times of immunogenicity and PK assessments will be agreed between the Sponsor and Investigator and documented in the Trial Master File (TMF).

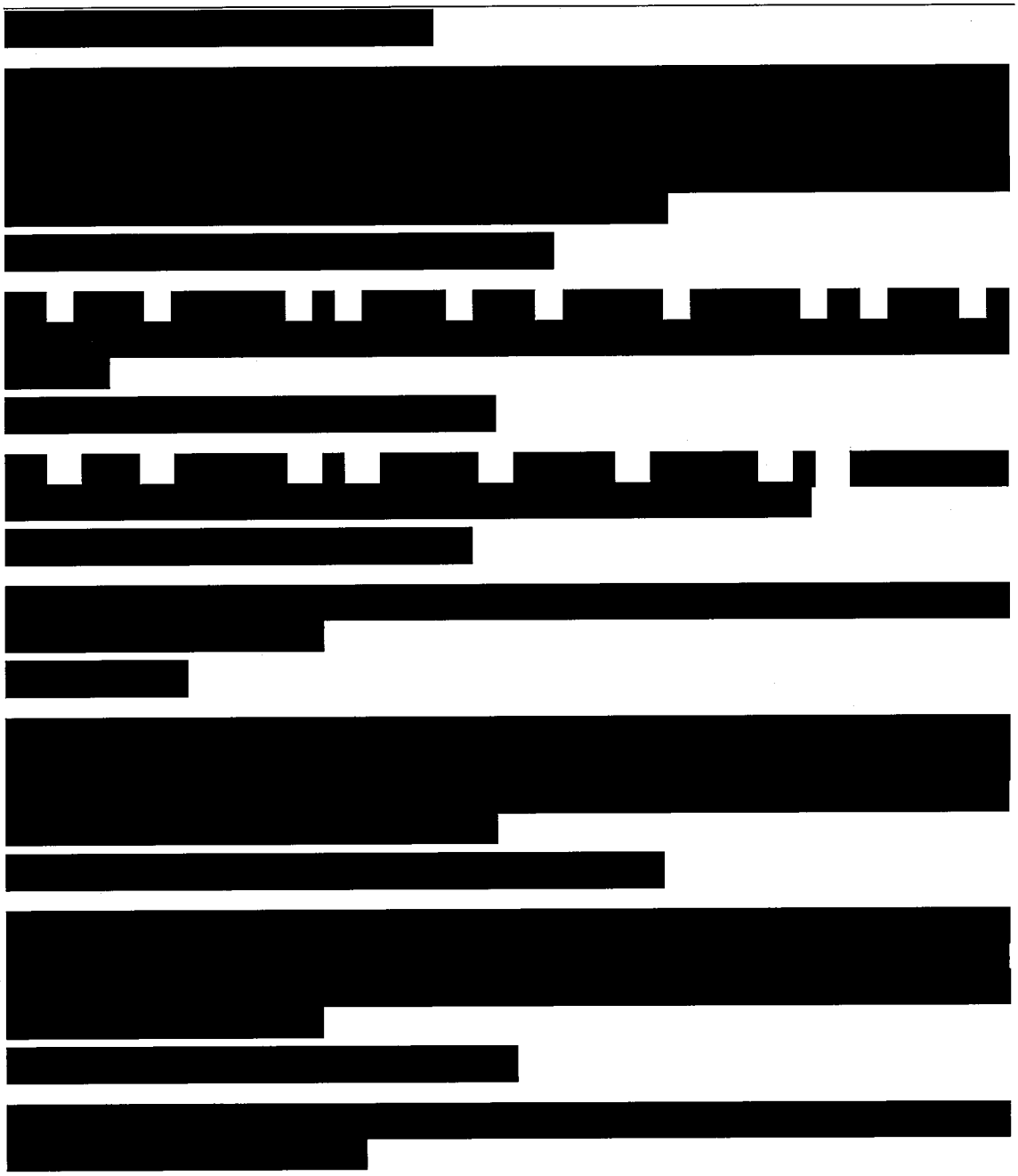
At agreed time points, immunogenicity and PK samples will be collected. Immunogenicity sample will be divided into anti-drug antibodies (ADA) and neutralizing antibody (NAb) sample. These samples will be packed in dry ice and sent by courier from the clinical site to the Central laboratory for later transmission to the analytical laboratories.

Contingency (back-up) ADA, NAb and PK samples will be retained at the clinical site and shipped separately to the primary samples.

PK analysis will be performed only on samples from subjects receiving MT-2990. ADA assay will be performed on all samples and NAb assay will be performed on ADA positive samples. Analyses will be performed using standard methods.

[redacted]

[redacted]



10.18 Safety Assessments

Refer to Section 12 for details of AE management.

10.18.1 Physical examination

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

[redacted]

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

10.18.2 Vital signs

Sitting blood pressure (systolic and diastolic) will be measured at all study visits, including Screening where vital signs are to be assessed. Sitting blood pressure will be measured using an automatic blood pressure recording device with an appropriate cuff size, after the subject has rested for at least 5 minutes in a sitting position. The same arm will be used for all measurements where possible. The Investigator will perform an overall evaluation of vital sign findings outside of the normal range for safety purposes; such results will be reported as either 'abnormal clinically significant (CS)', or 'abnormal not CS (NCS)'. Pulse rate and tympanic body temperature will also be measured. Abnormalities of clinical significance will be reported as AEs. Repeat measurements will be performed, if needed. In addition, at Visit 2, 5, 6 and 7, vital signs will also be measured at 15±5 minutes, 30±5 minutes and 60±10 minutes post study drug infusion.

10.18.3 Electrocardiogram

A 12-lead ECG (including HR and cardiac intervals: PR, QRS, QT, QTcF, and QTcB) 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. If required, the ECG may be reviewed by a specialist to evaluate for suspected abnormalities.

10.18.4 Transvaginal Ultrasound

A TVU will be performed outside menstruation during the Screening Period to identify clinically significant gynecologic condition as defined in the exclusion criteria [redacted] The Investigator will read the scan at Screening and decide whether the subject is eligible for the study or not.

10.18.5 Routine Laboratory Evaluations

Blood and urine samples will be collected for routine clinical laboratory safety evaluations during the study are presented in Table 4.

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

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

Table 4 Routine Laboratory Evaluations

Hematology:	
Hemoglobin	Mean corpuscular hemoglobin (MCH)
Hematocrit	Mean corpuscular hemoglobin concentration (MCHC)
Platelet count	Mean corpuscular volume (MCV)
Red blood cell (RBC) count	White blood cell (WBC) count and differential
Reticulocyte count	
Biochemistry:	
Alkaline phosphatase (ALP)	Cholesterol
Aspartate aminotransferase (AST)	Triglycerides
Alanine aminotransferase (ALT)	High density lipoprotein-cholesterol (HDL-C)
Gamma-glutamyl transpeptidase (GGT)	Low density lipoprotein-cholesterol (LDL-C)
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, hemoglobin	
Microscopic examination[1]	

[1] Performed only if required, based on urinalysis results

Blood and urine samples will be performed by the Central Laboratory using standard methods. Procedures for the handling of samples will be described in full in a separate document.

10.18.6 Total blood volume

The approximate total blood volume taken per subject is given in Table 5.

Table 5 Blood Volumes

Procedure	Sample volume (mL)	No. of samples	Total volume (mL)
Hematology	3.0	10	30.0
Biochemistry	4.0	10	40.0
Coagulation	3.0	10	30.0
PK	2.5	9	22.5
Measurement of anti-MT-2990 antibody	5.0	5	25.0
Biomarker (in serum)	7.0	5	35.0
		Overall total	**182.5**

Additional or repeat safety laboratory samples may be taken during the study if required by the Investigator.

[redacted]

10.20 Pharmacokinetic Assessments

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

For each PK assessment, 1 blood sample of approximately 2.5 mL will be collected to ensure there is sufficient serum for primary and contingency samples. Sample handling details will be described fully in a separate document.

10.21 Immunogenicity Assessments

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

For each immunogenicity assessment, 1 blood sample of approximately 5 mL will be collected to ensure there is sufficient serum for primary and contingency samples. Sample handling details will be described fully in a separate document.

11 STUDY DRUG/TREATMENT

11.1 Investigational Medicinal Product

11.1.1 Drug Product

[redacted]

11.1.2 Study Drug Supply

MT-2990 vials will be labeled and released according to GMP. All labeling will comply with applicable regulatory requirements. The Sponsor will provide all required release documentation for the finished product before it is dispatched.

The Sponsor will provide MT-2990 10 mL clear glass vials, fitted with fluoropolymer-faced butyl rubber stoppers and aluminum seals with pale green plastic flip-off caps to each site, for [redacted] for the duration of the subject's participation in the study. The unblinded pharmacist/trained designee will dispense a sufficient quantity of MT-2990 10 mL vials according to the subject's body weight consistent with each subject's dosage requirement and study visits according to the protocol.

Specifically, MT-2990 (each [redacted] vial of MT-2990) will be dispensed in a manner consistent with each subject's dosage requirement.

[redacted] which will be used for dispensing MT-2990 in a manner consistent with each subject's dosage requirement or will be used as placebo, will be sourced from a commercial supplier.

11.1.3 Formulation, Packaging, Site Storage, and Labeling

MT-2990 will be provided to the study sites in labeled vials. MT-2990 should be stored according to the IMP clinical label and [redacted] should be stored according to commercial labeling.

The labeling of MT-2990 10 mL vial (dispensing) will comply with applicable regulatory requirements. Appropriate volumes (according to the subject's body weight) of MT-2990 concentrate for solution for infusion will be withdrawn from the vial(s), and added to [redacted] The dispensed

MT-2990 [redacted] and placebo [redacted] without MT-2990) will be labeled. The dispensing, labeling and release will be performed and documented according to local requirements and procedures. The labeling will comply with applicable requirements.

Required study site documentation for MT-2990 vials will include, but may not be limited to, the following information:

- Receipt date
- Description of medication package, and medication product
- Lot number or code/Batch number or code
- Expiration and manufacturing dates
- Dispensing information
- Investigation New Drug number
- Certificate of compliance

11.1.4 Shipping, Receipt, Handling and Storage

On receiving a shipment of [redacted] at the Investigator site, the unblinded pharmacist/trained designee will conduct an inventory check and complete a supplies-receipt document via the Interactive Web-based Response System (IWRS), the original of which will be retained at the Investigator site. The unblinded pharmacist/trained designee will maintain a record of all [redacted] received and returned.

[redacted] at the Investigator site will be stored according to the conditions stated on the IMP clinical label and commercial label, respectively, in a locked, restricted-access area. The MT-2990 concentrate for solution for infusion should be allowed to reach ambient temperature before removing the required volume from the single use vial. A temperature log recording the daily maximum/minimum temperature of the storage area will be maintained (including weekends). Any storage temperature deviations of [redacted] will be reported to the Sponsor.

11.1.5 Dispensing

On each dosing occasion, a record of the "Study medication", [redacted] which will be dispensed to each subject, will be maintained by the unblinded pharmacist/trained designee on an accountability log. Any opened vials will not be re-used.

At each visit, the unblinded pharmacist/trained designee will prepare [redacted] with the subject allocated dose. [redacted] should be used within 4 hours at room temperature or within 24 hours at 5°C (±3°) of its preparation. Study

medication will be administered [redacted]

The Investigator or designee will be blinded to the study medication content and provide the subject with the dose [redacted] provided from the unblinded pharmacist/trained designee. A record of the study medication infused to each subject will be maintained by the unblinded pharmacist/trained designee on a Medication Accountability Log. Refer to instructions in the pharmacy manual.

11.1.6 Study Medication Accountability

The unblinded pharmacist/trained designee must maintain an accurate record of the shipment. During the study, the unblinded pharmacist/trained designee will record the quantities of study medication dispensed on an Accountability Log. All used vials and infusion bags must be retained for the purpose of drug accountability. The accountability (drug reconciliation) will be noted by the unblinded monitor during site visits and at the completion of the study. Study medication is to be used only for this Protocol and not for any other purpose.

11.1.7 Disposal and Destruction

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

[redacted] may be destroyed at the designated Sponsor facility or third party, as appropriate. Sites with documented drug destruction procedures and facilities may destroy drug on site with sponsor approval. Confirmation of destruction will be provided to the Sponsor.

A Sponsor designated facility will arrange for all used/unused MT-2990 vials and packaging to be destroyed according to local procedures and used/unused [redacted] to be destroyed after follow-up weighing upon return to the pharmacy according to local procedures once permission has been given by the Sponsor. Confirmation of destruction will be provided to the Sponsor.

Permission to return will only be given after all reconciliation has been completed and any queries closed. Authorization to destroy will be given when the Clinical Study Report (CSR) is signed, or as agreed with the Sponsor.

11.2 Dosing

The injection will be administered via [redacted] of approximately 250 mL, at a dose of MT-2990 [redacted] or placebo, over a period of approximately 45 minutes (± 5 minutes). The injection will be administered via 18 to 21-gauge cannula through a peripheral line. Following administration of study drug, [redacted] will be flushed with [redacted] to ensure that the entire dose is administered. An unblinded pharmacist/trained designee will reconstitute the MT-2990 injection for administration. MT-2990 injection will be dosed on an mg/kg basis. The dose to be delivered will be controlled by adjusting the total volume of injection.

Placebo is [redacted] and the volume of dose to be delivered should be same as with the total volume of MT-2990.

A description of the study medication dispensed are given in Table 6 and Table 7.

Table 6 Investigational Medicinal Product

	MT-2990 (Vial)
Dosage form	Concentrate for solution for infusion
Description	[redacted]
Strength	[redacted]
Storage conditions	The MT-2990 vials must be stored according to the conditions stated on the IMP clinical label. Keep the vials in the original carton until infusion preparation. The MT-2990 concentrate for solution for infusion should be allowed to reach ambient temperature before removing the required volume from the single use vial.

Table 7 Study Medication

	MT-2990 [redacted]	**Placebo** [redacted]
Dosage	[redacted]	Placebo to match active [redacted] bag dose
Route of administration	[redacted]	[redacted]
Treatment duration	[redacted]	[redacted]
Dosing instructions	The MT-2990 solution should be diluted with [redacted] Infusion should take place over approximately 45 minutes (± 5 minutes).	Infusion should take place over approximately 45 minutes (± 5 minutes).
Storage conditions (after dilution)	Within 4 hours at room temperature or 24 hours at 5°C (±3°) after dilution	Store according to commercial labeling

11.3 Compliance

Study medication will be administered by [redacted], according to the Protocol requirements, by designated qualified study personnel at the study site. The Investigator, or suitably qualified staff member, will supervise the administration of study medication and the exact time of dosing will be recorded in the subject's eCRF.

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

11.4 Subject identification

At Screening, the IWRS will assign each subject a unique Subject Identifier. The format of the unique Subject Identifier is A01-123-00345 where 123 is the 3-digit site number and 00345 is the 5-digit subject number, assigned uniquely, and sequentially to subjects across the study. The Subject Identifier will be used to reference the subject during the whole duration of the study. At the point of randomization, each subject will receive a unique Randomization Number. Both the Subject Identifier and the Randomization Number will be documented in the subject's source documents. The Subject Identifier will be recorded on study medication labels and other documentation.

A list identifying the subjects by their unique Subject Identifier and Randomization Number will be kept in the Investigator Site File.

11.4.1 Procedures for Assigning Subjects to Treatment Groups

Randomization will take place after confirmation of inclusion/exclusion criteria prior to the administration of study medication on Day 1. Subjects will be randomly allocated to 1 of 2 treatment groups (MT-2990 [redacted] or placebo) in a ratio of 1:1, according to an IWRS.

[redacted]

11.5 Maintenance of the Study Blind and Unblinding

Treatment will be double-blind; that is, neither the subject nor the Investigator site personnel except for unblinded pharmacist/trained designee will know which treatment is being taken. MT-2990 and placebo doses will be indistinguishable in volume and appearance in order to maintain the blind. Each subject's treatment will be labeled with a unique Subject Number, Initials, visit number and date. The IWRS will be used to hold treatment codes for each subject. The codes will only be accessible to authorized IWRS users. The IWRS should not normally be accessed with a request to break the treatment code for reasons other than safety or in an emergency. Should the Investigator wish to break the code for such reasons, he/she should ideally consult the Sponsor in advance. If this is not possible, the Investigator may access the IWRS to obtain the treatment code and provide the system with the reason for breaking the blind. The Sponsor should be notified as soon as possible thereafter. If the blind is broken for any individual subject, the subject must be withdrawn from the study, and any procedures accompanying withdrawal should be performed (refer to Table 2).

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).

Pharmacokinetic analysis will only be performed on samples from subjects receiving MT-2990; unblinded randomization codes will be given to the PK laboratory.

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

The dispensed MT-2990 [redacted] and placebo [redacted] will be prepared with identical appearance and suitably labeled to maintain the blind

12 ADVERSE EVENT MANAGEMENT

All AEs and SAEs will be recorded in the source documents. All SAEs that occur from the time written ICF is obtained until the end of the Double-blind Treatment Period (Visit 9), and all AEs that occur from Day 1 until the end of the Double-blind Treatment Period (Visit 9) 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 administration of study medication or if a predose illness increases in severity following dosing.

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

Post each study drug infusion, subject should be observed for approximately 60±10 minutes. During this period, vital signs must be obtained at 15±5 minutes, 30±5 minutes and 60±10 minutes. A patient instructions sheet will be provided to all subjects with instructions to observe and report all possible adverse events such as infusion related or infections in particular.

12.1 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 study medication. 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 a study medication, whether or not considered related to the study medication.

12.2 Adverse Events of Special Interest

AESIs will be collected for the following:

- All bone fractures

All AESIs (including event management and evaluation) will be recorded and reported similar to SAEs as described in Section 12.8. MT-2990 does not have any hormonal effects and is not anticipated to have any impact on bone mineral density. However, this population has been exposed to other hormonal treatments prior to study entry, increasing the risk of osteoporosis and possible fractures.

12.3 Definition of a Serious Adverse Event

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

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

Medical and scientific judgement should be exercised in deciding whether an AE is serious and whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or 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 (eg, 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 [TB] ward) is also counted as hospitalization.

SAEs will be recorded and reported as described in Section 12.8.

12.4 Severity of Adverse Events

The severity of AEs will be classified according to the following criteria: Mild: The event is transient and easily tolerated by the subject.

Moderate: The event causes discomfort and interferes with the subject's general condition.

Severe: The event causes considerable interference with the subject's general condition and may be incapacitating.

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

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

12.5 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.

12.6 Clinical Laboratory Abnormalities and Other Abnormal Assessments

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

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 CS abnormal laboratory results or assessments will be followed until they resolve (return to normal or Screening values) or stabilize, or until they are judged by the Investigator to be no longer CS.

12.7 Recording and Reporting of Adverse Events

All AEs, regardless of the relationship to study medication, occurring from Day 1, will be obtained from a subject until the end of the Double-blind Treatment Period (Visit 9) or the withdrawal of the subject from the study will be recorded.

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 Day 1.

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 12.4) and will assess the causality between the AEs and the study medication (as defined in Section 12.5).

Pre-existing illnesses, which started prior to entry and are still ongoing at the start of the study, will not be considered AEs unless they worsen during the Double-blind 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 Double-blind Treatment period, then they must notify the Sponsor immediately. This information does not require reporting of an AE on the eCRF, but should still be communicated to the Sponsor.

12.8 Recording and Reporting of Serious Adverse Events or Adverse Events of Special Interest

All SAEs occurring from the time written ICF is obtained from a subject until the end of the Double-blind Treatment Period or the withdrawal of the subject from the study must be reported to the Sponsor or the designee using the ***SAE/AESI Form in Clinical Study*** **within 24 hours** of the Investigator becoming aware of the SAE. All SAEs and AESI must also be entered in the AE section of the eCRF **within 24 hours.**

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

The reporting contact for SAEs/AESI is as follows:

[redacted]

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

[redacted]

The Sponsor will comply with the applicable regulatory requirements related to the reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the regulatory authorities and central IRB(s). The Investigator will be responsible for informing the local IRB(s) of relevant safety information, including SUSARs, as per local laws and requirements.

12.9 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 12.8) via a paper ***Pregnancy Notification Form in Clinical Study*** form. If the outcome or course of the pregnancy involves an SAE (eg, a congenital anomaly or spontaneous abortion), then the ***SAE/AESI Form in Clinical Study*** needs to be completed.

Subjects who become pregnant while on study should be withdrawn from treatment, as described in Section 8.5.

12.10 Follow-up of Adverse Events

The Investigator should follow-up with 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.

12.11 Reference Safety Information

The reference safety information for this clinical study is available in the MT-2990 Investigator's Brochure (IB).[12]

12.12 Overdose

There is no known antidote for MT-2990. 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 receives a dose which is greater or more frequent than 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 page of the 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 ***SAE/AESI Form in Clinical Study*** according to SAE/AESI reporting procedures (see Section 12.8).

13 DATA COLLECTION AND PROCESSING

13.1 Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) will convene to review safety data when;

a. 20 subjects are randomized and have completed the Week 2 visit
b. 50% of subjects are randomized and have completed the Week 4 visit
c. 50% of subjects are randomized and have completed the Week 16 visit

The independent DMC members will receive the list of AEs and SAEs every month and can request further information. All SUSARs will be reported in real time to the independent DMC, per expedited regulatory reporting timeframes (eg, 7 and 15 days). All subjects who are enrolled and received study medication will be included in the safety evaluations by the independent DMC at Weeks 2, 4, and 16.

13.2 Data Collection

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

Prior to the start of the study, the Investigator will complete a Delegation of Responsibility List. The Sponsor 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.

13.3 Case Report Form Completion

The Case Report Form 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.

13.4 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 14 and the Statistical Analysis Plan (SAP).

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

13.5 Patient Reported Outcomes

During the Screening and Double-blind Treatment period, subjects will complete a daily e-Diary using the electronic patient-reported outcomes (PRO) instrument. The PRO instrument will transmit the data to a technology database service provider, where it will store the electronic information. The data collected from the PRO database will be transferred to the Sponsor at database lock. At the EOS, each Investigator will receive a copy of the PRO data for subjects who were randomized at their site.

14 STATISTICAL METHODS AND PLANNED ANALYSES

14.1 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 to 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, based on results from the effect of [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.

14.2 Analysis Populations

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

- Randomized population will include all randomized subjects.
- Safety 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.
- PK population will include all randomized subjects who received at least 1 dose of MT-2990 and have at least 1 postdose value for plasma concentration without important protocol deviations, which may affect the PK of MT-2990.

14.3 Statistical Analysis

14.3.1 General Considerations

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

The statistical analysis will be performed using SAS® version 9.2 or higher. The ITT population will be used for all clinical efficacy analyses; the PP population will also be used for the primary and secondary efficacy endpoints for confirming robustness. The Safety population will be used for all safety summaries. PK assessments will be performed using the PK population.

All formal statistical tests will be done at the 5% 2-sided significance level. Point estimates will have 2-sided 95% confidence intervals (CIs) where applicable.

Where appropriate, variables will be summarized descriptively (frequency and percentage will be summarized for categorical variables; mean, SD, median, minimum, and maximum will be presented for continuous variables) by study visit and by treatment arm.

Statistical summaries will be presented for the changes from Baseline to each time point in efficacy endpoints where applicable.

All individual subject data will be listed.

14.3.2 Data Handling

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

14.3.3 Analysis of Demography and other Screening Subject Characteristics

Demographic and other Screening variables include age, sex, height, weight, ethnic origin, medical history, and concomitant medication.

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

14.3.4 Analysis Method

14.3.4.1 Primary Analysis

Change from Baseline to Weeks 4, 8, 12, and 16 in the monthly 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 as a covariate; weeks and treatment as fixed effect; subjects as random effect. Point estimates and 95% CIs for the difference between each active dose and placebo at Week 16 and other time points will be obtained.

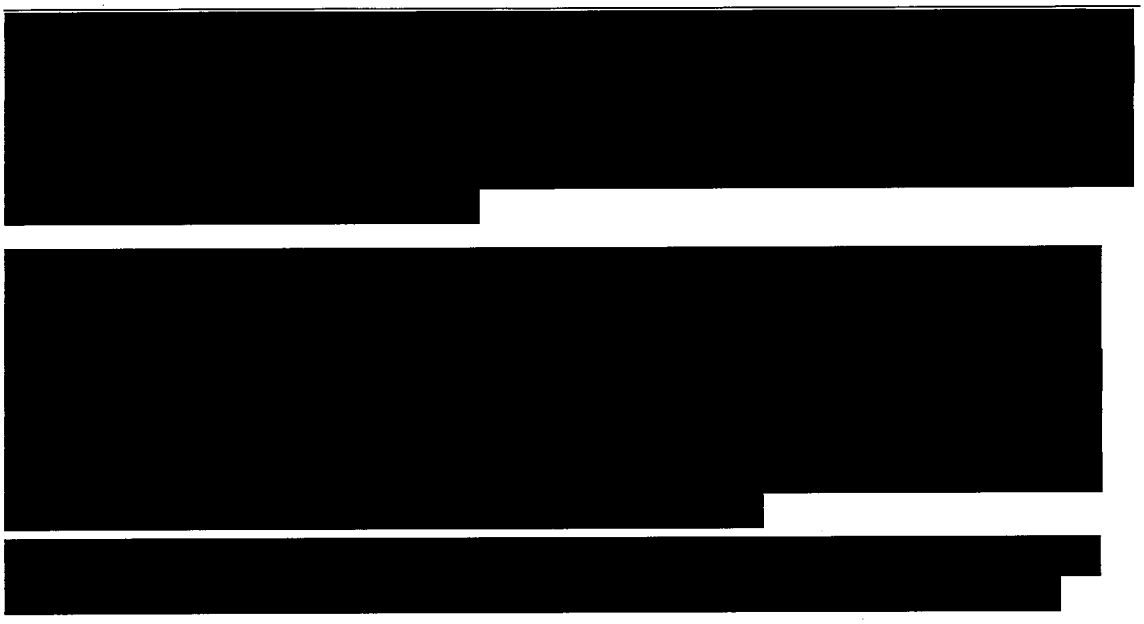
14.3.4.2 Secondary Analysis

Similar analysis to the primary analysis will be conducted for the primary endpoint using the last observation carried forward method for the missing value at or before the Week 16 visit

Similar analysis to the primary endpoint will be conducted to the key secondary endpoints.

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

[redacted]



14.3.4.3 Exploratory Analysis

Exploratory analysis may be performed. Details about exploratory analysis will be specified in the SAP.

14.3.4.4 Safety Evaluation

AEs are considered as treatment emergent if, they occur after the first dose administration of study medication or if a predose 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 arm 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. All fractures will be collected as AESI.

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

Other safety measures (eg, bone fractures, DEXA scan) will be summarized according to the data type.

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

14.3.4.5 Pharmacokinetic evaluation

All PK data will be listed and summarized using the number of observations, mean, SD, coefficient of variation (CV%), median, minimum, maximum, geometric mean, and geometric CV%. PK concentrations will be summarized by treatment and planned sampling time.

Population PK analysis will be performed using the plasma concentration of MT-2990 obtained in this study in combination with data obtained from other clinical studies. Population PK analysis results will be reported separately from the CSR. Details of the population PK analysis will be presented in a modelling plan.

14.3.4.6 Immunogenicity Evaluation

The proportion of subjects who develop antibodies against MT-2990 in serum will be summarized using descriptive statistics on the Safety Population. Further details will be provided in the SAP.

14.3.4.7 Other Data Evaluation

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

14.3.4.8 Exploratory Endpoint Evaluation

[redacted]

14.3.5 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.

15 STUDY MANAGEMENT AND ETHICAL AND REGULATORY REQUIREMENTS

15.1 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 of Technical Requirements of Pharmaceuticals for Human Use 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.

15.2 Investigator Responsibilities

15.2.1 Informed Consent Form

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

In the event that a subject is legally incompetent, the enrolment of such a subject should be in accordance with all applicable laws, and consent sought by the Investigator from the subject's legally authorized representative.

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

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

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

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

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

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

consent process with the amended ICF for any ongoing subjects.

15.2.2 Ethical and Regulatory Approval

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

1. Declaration of Helsinki, concerning medical research in humans (Adopted by the 18th World Medical Association [WMA] General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013).
2. ICH Harmonised Tripartite Guidelines for GCP 1996
3. Code of Federal Regulations Title 21

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

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

- Information on SUSARs
- Periodic reports on the progress of the study
- Notification of the EOS or ET
- Final study summary upon completion or closure.

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

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 IRBs 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/or IRB.

15.2.3 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 ICF 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.

15.2.4 Study Records Retention

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

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

15.2.5 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 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 IRB, regulatory authorities (as applicable), and assigned Clinical Monitor or Sponsor.

15.3 Data Monitoring Committee

An independent DMC, composed of experts in the management of subjects with the disease under study will be established for MT-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 analysis 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. 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. The planned interim analysis 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.

15.4 Central Reading of Transvaginal Ultrasound

The TVU will be performed locally by qualified personnel [redacted] The Investigator will read the TVU at Screening and will determine if the subject is eligible for the study.

15.5 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, enrollment rate, and data quality at the Investigator site. Through these visits and frequent communications (eg, 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 15.7.

15.6 Quality Assurance and Auditing

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

15.7 End of Study and site Closure

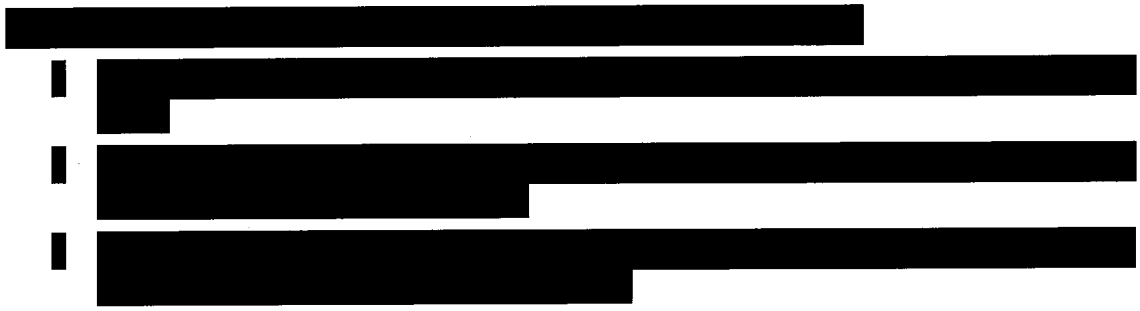
The EOS is defined as the last visit for the last subject. Upon completion of the study, or if the study or an Investigator site is prematurely discontinued, the following activities, where applicable, must be conducted by the Study Monitor in conjunction with the Investigator:

- Return of all study data to the Sponsor
- Completion of data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused MT-2990 and the [redacted]
- Review of Investigator site study records for completeness

Any unresolved AEs or SAEs will be followed according to Section 12.10.

15.8 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 noncompliance 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 per Table 2.

In addition, all general Investigator site activities required for the scheduled EOS and site closure should be completed as described in Section 15.7.

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

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

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

15.9 Liability and Insurance

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

16 DISCLOSURE OF DATA

16.1 Confidentiality

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

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

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

16.2 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.

17 REFERENCES

1. Liew FY, Girard JP, Turnquist HR. Interleukin-33 in Health and Disease. Nat Rev Immunol. 2016;16(11):676-689.

2. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity. 2005;23(5):479-90.

3. Moussion C, Ortega N, Girard JP. The IL-1-like cytokine IL-33 is constitutively expressed in the nucleus of endothelial cells and epithelial cells in vivo: a novel 'alarmin'? PLoS One. 2008;3(10):e3331.

4. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. Nat Rev Immunol. 2010;10(2):103-110.

5. Lu J, Kang J, Zhang C, Zhang X. The role of IL-33/ST2L signals in the immune cells. Immunol Lett. 2015;164(1):11-7.

6. Kyama CM, Debrock S, Mwenda JM, D'Hooghe TM. Potential involvement of immune system in the development of endometriosis. Reprod Biol Endocrinol. 2003;1;123.

7. Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. Fertil Steril. 2001;76(1):1-10.

8. Ahn SH, Monsanto SP, Miller C, Singh SS, Thomas R, Tayade C. Pathophysiology and Immune Dysfunction in Endometriosis. Biomed Res Int. 2015:1-12.

9. Santulli P, Borghese B, Chouzenoux S, Vaiman D, Borderie D, Streuli I, et al. Serum and peritoneal interleukin-33 levels are elevated in deeply infiltrating endometriosis. Hum Reprod; 2012;27(7):2001–2009.

10. Mbarik M, Kaabachi W, Henidi B, Sassi FH, Hamzaoui K. Soluble ST2 and IL-33: Potential markers of endometriosis in a Tunisian population. Immunol Lett. 2015:166:1-5.

11. Miller JE, Monsanto SP, Ahn SH, Khalaj K, Fazleabas AT, Young SL, et al. Interleukin-33 modulates inflammation in endometriosis. Sci Rep. 2017;7(1):17903.

12. MT-2990 Investigator's Brochure. Mitsubishi Tanabe Pharma Corporation, Version 2, 17 December 2017; addendum #1 to Version 3, 12 July 2018.

13. Ohnishi Y. Pharmacokinetic Study of MT-2990 after Single Intravenous Administration to Cynomolgus Monkeys. LSI Medience Corporation. Report No. B150626, 2016.

14. David H. MT-2990: Preliminary Toxicity Study by Weekly Intravenous Infusion or

subcutaneous administration to Cynomolgus Monkeys for 3 Weeks. Envigo CRS limited. Report No. NRM0023, 2016.

15. David H. MT-2990: Toxicity Study by Intravenous Infusion Administration to Cynomolgus Monkey for 4 Weeks Followed by a 4 Week Recovery Period. Envigo RS limited, Report No. LW45RG, 2016.

16. Ohnishi Y. A 4-week toxicokinetic study of MT-2990 in monkeys. LSI Medience Corporation. Report No. B160792, 2016.

17. Okamura T. A 26-week Intravenous Infusion Dose Toxicity Study of MT-2990 in Cynomolgus Monkeys Followed by a 4-week Recovery Period. LSI Medience Corporation. Report No. B170410, 2018.

18. Swithenbank C. Assessment of the Potential Cross-Reactivity of MT-2990 with a Selected Panel of Human and Cynomolgus Monkey Tissues. Covance Laboratories Ltd. Report No. 8339674, 2016.

19. Vincent K, Kennedy S, Stratton P. Pain scoring in endometriosis: entry criteria and outcome measures for clinical trials. Report from the Art and Science of Endometriosis meeting. Fertil Steril. 2010;93(1):62-67.

20. van Nooten FE, Cline J, Elash CA, Paty J, Reaney M. Development and content validation of a patient-reported endometriosis pain daily diary. Health Qual Life Outcomes. 2018;16(1):3.

21. Nirgianakis K, Bersinger NA, McKinnon B, Kostov P, Imboden S, Mueller MD. Regression of the inflammatory microenvironment of the peritoneal cavity in women with endometriosis by GnRHa treatment. Eur J Obstet Gynecol Reprod Biol. 2013;170(2):550-554.

22. Jones G, Kennedy S, Barnard A, Wong J, Jenkinson C. Development of an endometriosis quality-of-life instrument. The Endometriosis Health Profile-30. Obstet Gynecol. 2001;98(2):258-264.

23. Deal LS, Williams VS, DiBenedetti DB, Fehnel SE. Development and psychometric evaluation of the Endometriosis Treatment Satisfaction Questionnaire. Qual Life Res. 2010;19(6):899-905.

18 APPENDICES