STATISTICAL ANALYSIS PLAN

Study Titles:	LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3003
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	IND # 131161 EudraCT # 2017-003310-74
Version/Effective Date:	31-Jan-2020

STATISTICAL ANALYSIS PLAN APPROVAL SHEET

LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

This statistical analysis plan has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

31 Jan 2020
Date

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31 JAN 2020
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31 JAN 2020
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03 Feb 2020
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LIST OF ABBREVIATIONS

Term	Definition/Explanation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMD	bone mineral density
BMI	body mass index
BPD	Bleeding and pelvic discomfort
bpm	beats per minute
CI	confidence interval
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DXA	dual-energy x-ray absorptiometry
E2	estradiol
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
FP	feminine product
FPRR	feminine product return rate
HRQL	health-related quality of life
ICH	International Council on Harmonisation
LOCF	last observation carried forward
LS	least squares
MBL	menstrual blood loss
mITT	modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
msec	millisecond
NETA	norethindrone acetate
NRS	Numerical Rating Scale
PT	Preferred Term
QTcF	corrected QT interval Fridericia
SAP	statistical analysis plan
SD	standard deviation
SMQ	standard MedDRA query
SOC	System Organ Class
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
VAS	visual analogue score
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the efficacy and safety analyses planned for phase 3 study MVT-601-3003, entitled "An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids." Patients who completed study MVT-601-3001 (LIBERTY 1) or study MVT-601-3002 (LIBERTY 2) in one of three treatment arms: relugolix 40 mg + estradiol/norethindrone acetate (E2/NETA) 1 mg/0.5 mg for 24 weeks (Group A, also referred to as the relugolix + E2/NETA group), relugolix 40 mg for 12 weeks followed by 12 weeks of relugolix 40 mg + E2/NETA 1 mg/0.5 mg (Group B, also referred to as the relugolix + delayed E2/NETA group), or placebo for 24 weeks (Group C, also referred to as the placebo group) and meet eligibility criteria are enrolled in MVT-601-3003.

This SAP was developed in accordance with the International Council on Harmonisation (ICH) E9 guidelines.

This SAP is based on:

- Protocol MVT-601-3003, Amendment 1, dated 18 Oct 2018;
- ICH guidelines E3 (Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

The methods used for analysis of the MVT-601-3003 study are consistent with those used for the phase 3 studies (MVT-601-3001 and MVT-601-3002). This document may evolve over time (eg, to reflect the requirements of protocol amendments or regulatory requests). However, the SAP is to be finalized, approved by the sponsor, and placed on file before the database is locked. Changes to the final approved plan will be noted in the clinical study report (CSR).

1.1. Study Objectives and Endpoints

The objectives of Study MVT-601-3003 are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including 24 weeks of treatment during the parent study) of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks. The study objectives and endpoints are listed in Table 1. The endpoints in *italics* are not listed in the protocol, but they have been identified as important for assessment of treatment effect on the basis of emerging data and clinical relevance to the study objectives and therefore are included in this SAP.

Table 1: Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Efficacy	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women who achieve or maintain a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline to the last 35 days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on the following: o Achievement/maintenance of amenorrhea; o Hemoglobin; o Changes in symptom severity and quality of life related to uterine fibroids as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL); o Uterine volume; o Uterine fibroid volume.	• Change from parent study Baseline to Week 52 in menstrual blood loss (MBL); • Proportion of women who achieve or maintain amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve an increase of ≥ 1 g/dL from parent study Baseline at Week 52; • *Proportion of women with a hemoglobin ≤ 10.5 g/dL at parent study Baseline who achieve an increase of > 2 g/dL from parent study Baseline at Week 52;* • Change from parent study Baseline to Week 52 in hemoglobin; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score; • *Change from parent study Baseline to Week 52 in the UFS-QoL Bleeding and Pelvic Discomfort Scale score, a sub-*

Objective(s)	Endpoint(s)
	scale of the UFS-QoL Symptom Severity scale • Change from parent study Baseline to Week 52 in uterine volume; • Change from parent study Baseline to Week 52 in uterine fibroid volume.
Safety	
• To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including: o Adverse events; o Changes in bone mineral density.	• Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on estradiol.	• Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol.
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002).	• Change from parent study Baseline to Week 52 in the EQ-5D-5L.

Descriptive assessments of efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) on the extension study population, defined as patients who enrolled in MVT-601-3003 (i.e., who received at least one dose of study drug in the extension study), for the following treatment groups originally randomized in the parent studies:

- Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in the parent study;
- Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in the parent study;
- Parent Study Group C: Randomized to placebo in the parent study.

The parent study Baseline will be in general used as the reference point for the extension study for all change from baseline-related endpoints unless otherwise specified.

2. STUDY DESIGN

2.1. Summary of Study Design

The LIBERTY EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety extension study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1 mg and norethindrone acetate 0.5 mg for 28 weeks.

Approximately 600 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) with relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study.

Screening and baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study), which coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks.

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density (BMD) by DXA.

Patients who complete the study and are eligible may be enrolled in study MVT-601-035 at Week 52 visit after all Week 52 procedures for the MVT-601-3003 study have been completed. Patients who enroll directly into the MVT-601-035 study upon completion of the Week 52 visit will have the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recovery.

2.2. Sample Size Considerations

Because this is an extension study, the sample size will be determined by the numbers of patients who have completed either parent study (MVT-601-3001 or MVT-601-3002) and who are eligible and willing to participate in this study. No formal statistical testing has been planned.

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim safety analysis will be performed for the study at the time when at least 100 patients in the parent studies Group A (relugolix + E2/NETA treatment group) have completed the Week 52 study visit. At this timepoint, all patients enrolled in the extension study, regardless of their treatment assignment in the parent studies, will have completed their Week 36 study visit. The analysis cutoff date will be set as a date when at least 100 patients in the parent study Group A (relugolix + E2/NETA treatment group) complete the Week 52 study visit. Data from any assessments after this date will be excluded for this interim safety analysis.

3.2. Final Analyses

The final analysis of all efficacy and safety data from MVT-601-3003 will occur after all patients who entered the study have had the opportunity to be followed for 28 weeks of open-label treatment with relugolix + E2/NETA and through the 30-day safety follow-up visit.

3.3. Safety Follow-Up Analyses

Patients who are not proceeding into study MVT-601-035 and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy should be treated as per standard of care and additional follow up should be evaluated and managed, as needed, by a gynecologist. In addition, they should undergo a repeat biopsy in 3 to 6 months after the Week 52/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory.

Patients who are not proceeding into study MVT-601-035 and who have a BMD loss of > 3% at the lumbar spine (L1–L4) or total hip relative to the Baseline measurement at their Week 52/Early Termination visit occurring on or after Week 36 will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc.) that might affect BMD through the time of the repeat DXA scan. Patients who have a BMD loss of > 2% at the lumbar spine (L1-L4) or total hip relative to the Baseline measurement at their Early Termination visit occurring prior to Week 36 will also undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug. All follow-up DXA scans will be submitted for central reading.

Patients whose menses had not resumed as of the safety follow-up visit for unexplained reasons will be contacted by telephone to determine if menses have resumed.

Data collected during the additional safety follow-up period which is available at the time of database lock will be summarized and reported in the clinical study report. Complete data collected during the additional safety follow-up period will be summarized and reported in an addendum to the clinical study report.

4. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING OF MISSING DATA

4.1. Data Presentation Conventions

All statistical analyses will be conducted using SAS® Version 9.2 or higher.

All confidence intervals (CIs) will be reported as two-sided unless otherwise stated.

Where appropriate, variables will be summarized descriptively by study visit. For the categorical variables, the count and proportions of each possible value will be tabulated by parent study treatment group. For continuous variables, the number of patients with non-missing values, mean, median, standard deviation (SD), minimum, and maximum values will be tabulated.

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented to the same number of decimal places as the measured value. If the measured value is large (eg, > 100), fewer decimal places may be displayed.
- Percentages will be rounded to one decimal place;
- p-values will be rounded to four decimal places. p-values < 0.0001 will be presented as "< 0.0001" and p-values > 0.9999 will be presented as "> 0.9999";
- 1 month = 30.4375 days. Month is calculated as (days/30.4375) rounded to one decimal place;
- 1 year = 365.25 days. Year is calculated as (days/365.25) rounded to one decimal place;
- Age will be calculated using the date of randomization. If only year of birth is collected, 1 July of the year of birth will be used to calculate age.
- 1 pound = 0.454 kg;
- 1 inch = 2.54 cm;
- Missing efficacy or safety data will not be imputed, unless otherwise specified;
- For laboratory results above or below sensitivity limits displayed as "<" or ">," a quantification threshold, 0.0000000001, will be subtracted or added, respectively, to the threshold to derive a numeric result for analyses;
- For MBL volume reported as below the limit of quantification (for example, MBL below Quantification Level <5.0 mL or <2.5 mL), 0.0000000001 will be subtracted from the reported quantification threshold for the visit to derive a numeric result for analyses;
- For safety analyses, calculation of percentages will be calculated on the basis of the number of patients in the analysis population in each parent study treatment group;

- For by-visit observed data analyses, calculation of percentages will be calculated on the basis of the number of patients with non-missing data as the denominator, unless otherwise specified;
- For other continuous endpoints, the summary statistics will include mean, SD, median, and range (minimum and maximum);
- For categorical endpoints, the summary statistics will include counts and percentages;
- Confidence intervals, when presented, will generally be constructed at the 95% level. For binomial variables, exact methods will be employed, unless otherwise specified.

4.2. Analysis Populations

The protocol specified the efficacy analyses would be performed on the modified Intent-to-Treat (mITT) Population, defined as all patients who were randomized in a parent study and who have received any amount of study drug. Efficacy assessments up to 24 weeks of treatment of the mITT population in the parent studies will be presented in the Integrated Summary of Efficacy, therefore, they will not be included in the 3003 CSR. Efficacy data up to 52 weeks of treatment will be summarized in the Extension Study population defined below.

The protocol specified the safety analyses would be performed on the Safety Population, defined as all patients who were randomized in a parent study and who have received any amount of study drug. Safety assessments up to 52 weeks of treatment of all patients in the parent studies will be presented in the Integrated Summary of Safety. The open label CSR will only include safety data up to 52 weeks of treatment on the Extension Safety population as defined below.

4.2.1. Extension Study Population

The Extension Study population is defined as all patients who enrolled and received any amount of open-label study drug in study MVT-601-3003. All efficacy analyses will be performed using the Extension Study population, unless otherwise specified. Efficacy analyses will be performed by treatment group as randomized in the parent study.

4.2.2. Extension Safety Population

The Extension Safety population is defined as all enrolled patients who received any amount of open-label study drug in study MVT-601-3003. All safety analyses will be performed using the Extension Safety population, unless otherwise specified. Safety data will be analyzed by parent study treatment group according to the actual treatment received (not the randomized treatment). Any patient who received at least one dose of relugolix will be considered as a relugolix patient, consistent with analysis in the parent study.

4.3. Definitions, Computation, and Convention

4.3.1. Definition of Date of First Dose and Date of Last Dose of Parent Study Drug

The date of first dose of parent study drug is defined as the date when a patient receives the first dose of study drug (relugolix/placebo or E2/NETA/placebo) following randomization in study MVT-601-3001 or MVT-601-3002. The date of last dose of parent study drug is defined as the date a patient receives the last dose of study drug in the parent study, prior to or on the Week 24

visit date. The exact date of last dose of parent study drug will be known for all patients entering the MVT-601-3003 study.

4.3.2. Definition of Date of First Dose and Date of Last Dose of Extension Study Drug

The date of first dose of extension study drug is defined as the date when a patient receives the first dose of open-label study drug (relugolix or E2/NETA) in the MVT-601-3003 study. The date of last dose of extension study drug is defined as the date a patient receives the last dose of open-label study drug in the MVT-601-3003 study. If the complete date of last dose of extension study drug is unknown, the last date the extension study drug was dispensed will be used. For patients missing only day for date of last dose of extension study drug, either first of the month of last dose of extension drug or last date extension study drug was dispensed will be used, whichever is later.

4.3.3. Study Day

Study day will be calculated with respect to the date of the first dose of study drug in the parent study (Study Day 1). For assessments conducted on or after the date of the first dose of parent study drug, study day will be calculated as:

(Assessment date – date of first dose of parent study drug) + 1

For assessments conducted before the date (and time) of the first dose of parent study drug, study day will be calculated as:

(Assessment date – date of first dose of parent study drug)

4.3.4. Extension Study Day

Extension study day will be calculated with respect to the date of the first dose of open-label study drug in the extension study (Extension Study Day 1). For assessments conducted on or after the date of the first dose of extension study drug, extension study day will be calculated as:

(Assessment date – date of first dose of extension study drug) + 1

For assessments conducted before the date (and time) of the first dose of extension study drug, extension study day will be calculated as:

(Assessment date – date of first dose of extension study drug)

For patients who do not receive any amount of extension study drug, extension study day will be calculated as above with respect to the date of enrollment in the extension study.

4.3.5. Definition of Treatment Duration

Overall treatment duration is defined as the duration of time from the date of the first dose of parent study drug to the date of the last dose of extension study drug as follows:

(Date of last dose of extension study drug – Date of first dose of parent study drug) + 1

For patients missing day and month for date of last dose of extension study drug, the last date extension study drug was dispensed will be used to calculate treatment duration. For patients missing only day for date of last dose of extension study drug, the later of first of the month of

last dose of extension drug or last date extension study drug was dispensed will be used to calculate treatment duration.

4.3.6. Definition of Extension Study Treatment Duration

Treatment duration in the extension study is defined as the duration of time from the date of the first dose of extension study drug to the date of the last dose of extension study drug as follows:

(Date of last dose of extension study drug – Date of first dose of extension study drug) + 1

For patients missing day and month for date of last dose of extension study drug, the last date extension study drug was dispensed will be used to calculate treatment duration. For patients missing only day for date of last dose of extension study drug, the later of first of the month of last dose of extension drug or last date extension study drug was dispensed will be used to calculate treatment duration.

4.3.7. Definition of Baseline Value and Post-Baseline Value

Unless otherwise specified, Baseline values are defined as the last measurement before the first administration (date and time) of study drug in the parent study. A post-Baseline value is defined as a measurement taken after the first administration of study drug. Change from Baseline is defined as (post-Baseline value – Baseline value). Both date and time of study drug administration and measurement will be considered when calculating Baseline value. If the time is not available, then the date alone will be used. For patients who receive no study medication, the date of randomization will be used in place of the date of first dose in determining Baseline and post-Baseline values.

4.3.8. Visit Windows

Visit windows, which will be used to associate assessments with a scheduled visit, will be used only for summarizing data by visit. The windows for scheduled assessments are shown in Table 2, Table 3 (BMD), Table 4 (electrocardiogram [ECG]), Table 6 (UFS-QoL), and Table 6 (transvaginal ultrasound and EQ-5D-5L) respectively. For safety assessments, the study day will be used to determine the associated visit window. There will be no separation of data from the parent and extension study. For example, if an assessment in the extension study falls in the Week 24 visit window, it will be summarized as Week 24.

If the results from more than one assessment are within a given visit window, the non-missing result from the assessment closest to the target date will be used. If two assessments are equally close to the target day, the earlier assessment will be used. For summaries of shift from Baseline in safety parameters, all values will be considered for these analyses.

Table 2: Visit Windows for Monthly Assessments

Visit	Start Day	Target Day	End Day
Week 4[a]	1	29	43
Week 8	44	57	71
Week 12	72	85	99
Week 16	100	113	127
Week 20	128	141	155
Week 24	156	169	183
Week 28	184	197	211
Week 32	212	225	239
Week 36	240	253	267
Week 40	268	281	295
Week 44	296	309	323
Week 48	324	337	351
Week 52	352	365	Date of last dose + 6[b]
Safety Follow-Up[c]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

[a] Start day of Week 4 for study day 1 includes only post-Baseline assessments that occurred after the first dose.

[b] End day of Week 52 is date of last dose + 1 for patients entering the MVT-601-035 study.

[c] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 3: Visit Windows for Bone Mineral Density Assessments

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Week 36	197	253	308
Week 52	309	365	421

Assessments will be excluded from analysis if they occur on or after the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids. Assessments after date of last dose of extension study drug + 30 days will also be excluded from analysis.

Table 4: Visit Windows for Week 12, 24, and 52 Assessments (ECG)

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Week 52	309	365	421

Table 5: Visit Windows for Week 12, 24, 36, and 52 Assessments (UFS-QoL)

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Week 36	197	253	308
Week 52	309	365	421
Safety Follow-up[a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

[a] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 6: Visit Windows for Week 24 and 52 Assessments (Transvaginal Ultrasound, EQ-5D-5L, Endometrial Biopsies)

Visit	Start Day	Target Day	End Day
Week 24	128	169	196
Week 52	309	365	421
Safety Follow-up[a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

[a] The safety follow-up visit window will be restricted to assessments prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids.

Table 7: Time Window for Feminine Product Collection

Visit	Feminine Product Collection Visit Date[a,b]	Time Window[a]
Week 28	X_1	(Date of Extension Study Day 1) - < X_1
Week 32	X_2	(X_1 +1) - ≤ X_2
Week 36	X_3	(X_2 +1) - ≤ X_3
Week 40	X_4	(X_3 +1) - ≤ X_4
Week 44	X_5	(X_4 +1) - ≤ X_5
Week 48	X_6	(X_5 +1) - ≤ X_6
Week 52/EOT	X_{Last}[c]	(Previous Feminine Product Returned Visit +1)] – ≤ X_{Last}

[a] If feminine products are collected at more than 1 visit within a given visit window (Table 2), the last feminine product collection date will be used to define the time window. If the patient missed the previous visit, a planned study visit date will be used to calculate the window.

[b] In the absence of feminine product collection due to amenorrhea the visit date when amenorrhea was reported will be used.

[c] Date of last non-missing feminine product collection within the interval from (last dose date – 35) to (last dose date + 7 days) (see Section 7.2.2).

General Rules for Missing Data

Handling of missing data for the primary efficacy analysis is described in Section 7.2.4.

4.3.9. By-Visit Endpoints

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

4.3.10. Adverse Events and Concomitant Medications

The following imputation rules for the safety analyses will be used to address the issues with partial dates. The imputed dates will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end dates of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default.

The following rules will be applied to impute partial dates for adverse events:

- If start date of an adverse event is partially missing, impute as follows:
  - If both Month and Day are missing and Year = Year of parent study treatment start date, then set to parent study treatment start date, as long as adverse event end date is not prior to parent study treatment start date;
  - If both Month and Day are missing and Year ≠ Year of parent study treatment start date, then set to January 1;

  - If Day is missing and Month and Year = Month and Year of parent study treatment start date, then set to parent study treatment start date, as long as adverse event end date is not prior to parent study treatment start date;
  - If Day is missing and Month and Year ≠ Month and Year of parent study treatment start date, then set to first of the month;
  - If start date is completely missing, set to parent study treatment start date, as long as adverse event end date is not prior to parent study treatment start date.
- If end date of an adverse event is partially missing, impute as follows:
  - If both Month and Day are missing, then set to December 31;
  - If only Day is missing, then set to last day of the month;
  - If end date is completely missing, do not impute.

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both).

The following rules will be applied to impute partial dates for medications:

- If start date of a medication is partially missing, impute as follows:
  - If both Month and Day are missing, then set to January 1;
  - If only Day is missing, then set to the first of the month.
- If end date of a medication is partially missing, impute as follows:
  - If both Month and Day are missing, then set to December 31;
  - If only Day is missing, then set to last day of the month.

If start date or end date of a medication is completely missing, do not impute.

5. STUDY POPULATION

5.1. Subject Disposition

The number of patients for each of the following categories will be summarized by parent study treatment group:

- All patients enrolled in the Extension Study;
- Patients included in the Extension Safety population;
- Patients who completed the 28-Week open-label treatment period;
- Patients who discontinued early from the 28-Week open-label treatment period and reasons for discontinuation;
- Patients who enrolled in study MVT-601-035.

5.2. Protocol Deviations

Protocol deviations that occurred during the extension study will be categorized as important or minor per the protocol deviation plan. Important protocol deviations will include, but will not be limited to, the following categories:

- Patient treated with open-label study drug who did not satisfy key entry criteria;
- Patient treated with open-label study drug who met withdrawal criteria during the study but was not withdrawn;
- Patient treated with open-label study drug who received a prohibited concomitant medication that met criteria for an important protocol deviation.

Important protocol deviations will be summarized by deviation category for all patients in the Extension Safety population. A patient listing of all important protocol deviations will be provided.

5.3. Demographic and Baseline Characteristics

Demographic and Baseline characteristics will be summarized by parent study treatment group assignment for the Extension Safety population. Categorical data will be summarized using frequencies and percentages, by parent study treatment group and overall (see Table 8 below). Summaries of continuous data will display the mean, SD, median, minimum, and maximum. The numbers of missing values will also be summarized.

Table 8: Categories for Demographic and Baseline Characteristics

Variable	Category
Age (years)	< 40, ≥ 40
Geographic region	North America, Rest of World
Race	Black or African American, White, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino, or Not reported
BMI (kg/m^2) at Baseline	< 18.5, 18.5 to <25, 25 to <30, 30 to < 35, 35 to < 40, ≥ 40
History of prior pregnancy	Yes, No
Disease duration of uterine fibroid (years)	Min to <1, ≥ 1 to < 3, ≥3 to <5, ≥5 to <10, ≥ 10
Type of uterine fibroids	
Subserous fibroid	Yes, No
Intramural fibroid	Yes, No
Submucosal fibroid	Yes, No
Other	Yes, No
Any surgery for uterine fibroids	Yes, No
Volume of myoma at Baseline (cm^3)	< 25, ≥ 25
Volume of uterus at Baseline (cm^3)	< 300, ≥ 300
Menstrual blood loss volume at Baseline (mL)	< 225, ≥ 225
Menstrual blood loss volume at Baseline (mL)	< 160, ≥ 160
Hemoglobin at Baseline (g/dL)	Min to < 8, ≥ 8 to <10.5, ≥ 10.5 to <12, ≥ 12
UFS-QoL Bleeding and Pelvic Discomfort Scale	0 to < 25, 25 to <50, 50 to <75, 75 to 100
Maximum NRS score for uterine fibroid-associated pain at Baseline	< 4, ≥ 4
Patient Global Assessment	
Function	No limitation at all, Mild limitation, Moderate limitation, Quite a bit of limitation, Extreme limitation
Symptoms	Not severe, Mildly severe, Moderately severe, Very severe, Extremely severe

Abbreviations: BMI = body mass index; NRS = Numerical Rating Scale; UFS-QoL = Uterine Fibroid Symptom and Health-Related Quality of Life.

5.4. Medical History

Medical history collected at the time of entry into the parent study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be summarized by system organ class (SOC) and preferred term (PT) for the Extension Safety population. Additionally, summaries of uterine fibroid–specific medical and surgical treatment history collected at the time of entry into the parent study will be provided. A patient with multiple occurrences of medical history within a PT will be counted only once in that PT.

5.5. Prior Medications and Concomitant Medications

Prior medications and concomitant medications taken during the parent and extension study treatment period will be summarized for all patients in the Extension Safety population by parent study treatment group. Medications are considered concomitant if exposure occurs during the parent or extension treatment period. Medications are considered prior if exposure started prior to the date of first dose of parent study drug.

The number and percentage of patients who took at least one dose of a prior medication for treatment of uterine fibroids will be summarized by parent study treatment group and overall using the World Health Organization (WHO) Drug Dictionary and summarized according to the Anatomical Therapeutic Chemical (ATC) Classification System and generic medication name. A patient who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6. STUDY DRUG EXPOSURE AND COMPLIANCE

All analyses of extent of exposure to study drug and compliance will be summarized by actual treatment received in the parent study. Extent of exposure to relugolix and E2/NETA during the extension study will be summarized for patients in the Extension Safety population. Overall exposure to relugolix (with or without E2/NETA), overall exposure to E2/NETA, and overall exposure to any study drug (relugolix [with or without E2/NETA] and placebo) throughout the parent study and extension study will be summarized by parent study treatment group. Compliance with open-label study drug during the extension study for the Extension Safety population will be summarized by parent study treatment group. Overall compliance with study drug throughout the parent study and extension study will be summarized by parent study treatment group. Exposure to and compliance with relugolix and E2/NETA will be summarized separately and will be based on the drug accountability case report forms.

Study drug exposure summaries will include the total dosage of relugolix and E2/NETA taken in milligrams and treatment duration. Total dosage of relugolix and E2/NETA taken during the extension study and overall, throughout the parent and extension studies, will be summarized by parent study treatment group. Treatment duration during the extension study and overall with any study drug (relugolix, E2/NETA, or placebo) will be summarized by parent study treatment group.

Study drug compliance will be summarized for the extension study treatment period and for the overall parent and extension study treatment period, and will be calculated as follows:

(total tablets taken / total tablets expected to be taken) × 100

The total tablets taken will be calculated as:

(total tablets dispensed - total tablets returned)

The total tablets expected to be taken is calculated as the total number of tablets a patient is expected to take each day times the length of time (in days) that the patient was in the treatment period of the study. Tablets that were dispensed and not returned will be assumed to have been taken. For patients who did not return for their last scheduled visit, tablets that were dispensed and not returned will not be included in the calculation of study drug compliance. For patients who did not return for any extension study visits after week 24 and did not return dispensed extension study drug, extension study drug compliance will not be calculated and will be categorized as “not able to calculate” in summaries of extension study drug compliance.

Summary statistics of study drug compliance (eg, mean, median, etc.) will be presented, along with a categorical summary (eg, < 80%, 80% to 100%, > 100%).

7. EFFICACY ANALYSES

7.1. General Considerations

Efficacy analyses will be conducted on the Extension Study population according to the parent study randomized treatment assignment. Stratified analyses will incorporate the randomization stratification factors. If the group of patients at any factor level from a randomization stratification factor (eg, patients with Baseline MBL volume ≥ 225 mL) comprises < 10% of the entire mITT population, this stratification factor (eg, Baseline MBL volume) will not be used for stratified analyses. In addition, if there are < 15 patients in 1 of the 4 strata (derived from the 2 stratification factors each with 2 levels), only stratification factor of Baseline MBL volume (< 225 versus ≥225 mL) will be used in the stratified analysis for more robust strata-adjusted estimation of treatment effect. The stratification category used at the time of randomization (in the Interactive Web Recognition Service [IWRS] system) will be used for all analyses rather than data recorded on the electronic case report form (eCRF) unless otherwise specified.

No formal treatment comparisons will be performed for this extension study. As there is no inferential statistics for this analysis, there is no need for multiplicity adjustment.

7.1.1. Analyses for Categorical Data

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise specified, the calculation of proportions will include the missing category. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

For efficacy endpoints evaluating proportions descriptive statistics (point estimates and corresponding 95% CIs) will be provided by treatment group and visit as appropriate.

7.1.2. Analyses for Continuous Data

Continuous variables will be summarized using descriptive statistics (eg, n, mean, median, SD, minimum, and maximum). For the analyses of change from Baseline, the mean at Baseline will be calculated for all patients with at least one post-Baseline value by treatment group. Additionally, the mean will also be calculated for each visit, including only the patients who are in the analysis who have data for that visit by treatment group.

For endpoints evaluating the change (absolute or percent change) from Baseline to Week 52, mean change as well as least squares (LS) means change and 95% CI will be summarized. LS means and 95% CI will be derived separately for each treatment group using a mixed model repeated measures approach with randomization stratification factors included as fixed effects. The Baseline value will be included as a covariate, and an unstructured variance-covariance matrix will be assumed. If the mixed model fails to converge, a first-order autoregressive variance-covariance matrix will be used. Calculation of the dependent variable (change from Baseline) for each patient at each visit will be calculated based on the visit windows specified in Section 4.3.8. In addition, summary statistics (mean change or mean % change) will be graphically presented as appropriate.

7.2. Primary Efficacy Endpoint

The primary efficacy endpoint of the study is the proportion of women who achieve an MBL volume of < 80 mL AND at least a 50% reduction from parent study Baseline in MBL volume over the last 35 days of treatment as measured by the alkaline hematin method. The primary endpoint will be referred to as responder rate and derived on the basis of the total MBL volume measured at the Week 52/EOT visit window taking into consideration the patient's compliance with return of feminine products and completion of the paper patient Diary (see Section 7.2.3 for details). For the primary analysis, primary endpoint will incorporate the missing data handling rules described in Section 7.2.4.

7.2.1. Primary Efficacy Analysis

The responder rate and two-sided 95% CI will be presented for each treatment group.

7.2.2. Definitions Related to Menstrual Blood Loss

The data sources that will be used to support derivation of responder status include:

- Menstrual blood loss volume determined by the alkaline hematin method;
- Daily patient report of bleeding (yes/no) and use of feminine product (yes/no) captured in the paper patient Diary;
- The status of feminine product (FP) collection return (yes/no) recorded on the electronic case report form (eCRF) page at each visit with specific reasons captured when no product collection was returned.

The total MBL volume is reported from the analysis of FP returned for each collection interval. An inventory of days (with dates) for which FP was collected and returned is also available. This inventory is aligned with patients' reports of bleeding and FP use in the paper patient Diary. The status of FP collection return, and specifically the reason for non-return of FP reported on the Feminine Product Collection eCFR page is used to support derivation of responder status (see Section 7.2.4 for details).

7.2.2.1. Menstrual Blood Loss Volume

All returned feminine products (validated, validated but unauthorized, or unvalidated products) collected at each visit will be analyzed by the alkaline hematin method to obtain the MBL volume. The MBL volume measured over the Week 52/EOT feminine product collection interval (up to 35 days prior to the last dose of treatment) will be used for analysis of the primary efficacy endpoint (see details below). The vendor, KCAS, reports when unauthorized feminine products (products not dispensed for use in the trial) have been returned. KCAS also reports whether the unauthorized products have previously been validated for their analysis. The report details MBL volumes for authorized, unauthorized but validated, and unauthorized and unvalidated products.

7.2.2.2. Baseline Menstrual Blood Loss Volume

Baseline MBL volume is defined as the average MBL volume from the one or two consecutive screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of parent study drug as assessed by the alkaline hematin method as follows:

For patients with MBL volume ≥ 160 mL during the screening period, the Baseline MBL volume is the last measurement collected before the first administration of parent study drug.

If the MBL volume is < 160 mL, the Baseline MBL volume is defined as the average of the MBL volume from the two screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of parent study drug as assessed by the alkaline hematin method (see Figure 4-2 of the study protocol MVT-601-3001/3002 for details).

7.2.2.3. Week 52/EOT Feminine Product Collection Interval

To ensure collection of all feminine products used during that menstrual cycle, an interval of up to 35 days for measurement of the primary endpoint was selected to accommodate women who continue to have cyclic bleeding on study treatment and whose natural cycle was at the upper end of the normal cycle duration range. This method is consistent with that used during screening for collection of feminine products and with that used for the primary efficacy analysis in the parent studies. Specifically, the feminine product collection interval at Week 52/EOT is driven by types of bleeding patterns experienced by the patients, as described below:

- For patients who continue to have cyclic bleeding, the length of the interval depends on the duration of the patient's natural cycle; this is consistent with the way the Baseline MBL volume was determined (eg, the interval ranging from approximately 21 to 35 days);
- Patients who report irregular, non-cyclic bleeding are instructed to collect and return all feminine product used between study visits, up to 35 days, as per the schedule of events;
- For patients who report amenorrhea on the feminine production collection eCRF page, an interval of last 35 days of treatment will be reviewed to ensure that reported amenorrhea is not due to incomplete collection.

For patients who are in the midst of an episode of cyclic bleeding at the time of the Week 52/EOT visit, the visit window may be extended up to 7 days after the last dose of study drug to ensure patients return all used feminine products over that bleeding episode.

Per protocol, all used feminine products are to be collected at each visit and returned for analysis using the alkaline hematin method. For patients who continue to have menstrual bleeding, study visits are timed such that the feminine products used in the entire menstrual bleeding cycle are collected in one container provided at each visit.

7.2.2.4. MBL Volume at Week 52/EOT

MBL volume at Week 52/EOT is defined as the MBL volume obtained from the feminine product returned over the Week 52/EOT feminine product collection interval, as described above. The MBL volume at Week 52/EOT will be used to derive the primary efficacy endpoint.

If a patient did not return feminine product over the last 35 days of treatment and reported amenorrhea on the feminine product return eCRF page, she will be considered as amenorrhoeic and her MBL volume will be assigned as 0 mL.

7.2.2.5. Feminine Product Return Rate at Week 52/EOT

To quantify degree of compliance with feminine product collection, the FPRR will be calculated based on the inventory of feminine product returned by day (dates) summarized on the Feminine Product Collection eCFR page (provided by the vendor, KCAS) and responses to the paper patient Diary questions regarding bleeding experience and the use of feminine product obtained for the corresponding Diary window (see Table 7). Specifically:

- For those who returned feminine product at Week 52/EOT, the FPRR was calculated as the observed number of days with returned feminine products (based on the inventory of FP received by KCAS) divided by the expected number of days with bleeding and use of product as reported on the patient's paper Diary within the Week 52/EOT feminine product collection interval (as defined above).
- For those who did not return any feminine products:
  - If the reason was amenorrhea reported on the eCRF or if spotting/negligible bleeding was reported on the eCRF and confirmed by patient's paper Diary over the Week 52/EOT visit window, their FPRR will be set to 100% because the lack of menstruation obviates the need for feminine product collection.
  - Otherwise if the reason is any other, their FPRR was set to 0.

$$\text{FPRR} = \frac{\text{observed (No. of days with returned FP [per KCAS])}}{\text{expected (No. of days reported bleeding and use of FP [per Diary])}} x100$$

7.2.3. Definition of Responder Status at Week 52/EOT

A responder at Week 52/EOT is defined as a patient who satisfies both the following:

- Had MBL volume of < 80 mL at Week 52/EOT;
- Had at least a 50% reduction from Baseline in MBL volume at Week 52/EOT.

The reduction from Baseline in MBL volume at Week 52/EOT will be calculated as the absolute change at Week 52/EOT in MBL volume from the Baseline MBL volume divided by the Baseline MBL volume.

Responder status at Week 52/EOT will be assessed based on the reported MBL volume at Week 52/EOT, in conjunction with treatment duration, compliance with feminine product collection, and compliance with paper patient Diary entry over the same visit window (see Section 7.2.4 for details).

7.2.4. Missing Data Handling Rules

For the evaluation of the primary endpoint, missing data handling rules will be implemented to derive responder status at Week 52/EOT as described below. The following elements will be checked: compliance with feminine product collection against the patient's paper Diary, as measured by FPRR; compliance with patient's paper Diary entry, defined as the proportion of Diary entry days over the length (days) of FP collection interval for Week 52/EOT visit; and reasons for no FP collection (as displayed in Table 9).

Last Observation Carried Forward (LOCF) Approach

The latest non-missing MBL volume (ie, LOCF), including 0 mL for confirmed amenorrhea or confirmed spotting or negligible bleeding, will be used as Week 52/EOT MBL volume to determine response status. LOCF will not be used to determine response status for patients who withdraw from the extension study prematurely due to lack of efficacy or to undergo surgical intervention for uterine fibroids. These patients will be considered non-responders. Patients missing MBL volume for all visits in the extension study will carry forward their Week 24/EOT responder status from the parent study as their Week 52/EOT responder status.

FPRR will be applied at Week 52/EOT to determine response status as described below. FPRR will not be considered when using prior observed MBL volume to determine response status. The observed MBL volume from the prior visit will be used to determine response at Week 52/EOT.

To determine response status at Week 52/EOT:

- Patients who withdraw from the extension study prematurely due to lack of efficacy or to undergo surgical intervention for uterine fibroids will be considered non-responders;
- For patients with a FPRR of 100%, responder status will be determined based on the observed MBL volume;
- For patients who had incomplete feminine product collection, with a FPRR of < 100%, responder status will be derived based on either LOCF or observed MBL volume as follows:
  - Those with an MBL volume ≥ 80 mL or < 50% reduction from Baseline will be considered non-responders;
  - Those with an MBL volume < 80 mL and ≥ 50% reduction from Baseline will be considered **partial or complete missing MBL volume. LOCF observed MBL volume will be used to determine response status.**
- For patients who did not return a feminine product collection, responder status will be determined depending on the reason reported on the Feminine Product Collection eCRF:
  - If the reason is reported as Amenorrhea, the last 35 days of treatment will be used to derive responder status:
    - If the Week 52/EOT interval was 35 days, then she will be considered as a responder;

- If the Week 52/EOT interval was <35 days, the following supportive information will be used to derive responder status:
  - If a patient reported amenorrhea at the visit prior to Week 52/EOT, she will be defined as a responder;
  - If a patient did not report amenorrhea at the visit prior to Week 52/EOT, paper Diary data from the prior visit interval will be reviewed to confirm whether the patient was amenorrheic for a total of 35 days.
    - If the paper Diary from the previous interval confirms amenorrhea, then the patient will be considered as a responder;
    - Otherwise, **MBL volume will be considered missing and LOCF observed MBL volume will be used to determine responder status**.

- If the reason is Other and the specification describes spotting or negligible bleeding, responder status will be defined as follows:
  - The patient will be considered as a responder if it is supported by the paper Diary data: the paper Diary entry rate must exceed 70% and the patient must have reported no more than 5 total days of bleeding with product use and no more than 3 consecutive bleeding with product use over the collection interval.
  - If the paper Diary entries did not confirm spotting or negligible bleeding, **MBL volume will be considered missing and LOCF observed MBL volume will be used to determine responder status.**

- If the reason is any Other, the responder status will be derived as follows:
  - **MBL volume will be considered missing. LOCF observed MBL volume will be used to determine responder status**.

- Patients with no visit within the FP collection interval for Week 52/EOT. **MBL volume will be considered missing and LOCF observed MBL volume will be used to determine responder status.**

Table 9: LOCF Approach for Derivation of Responder Status at Week 52/EOT and Missing Data Handling Rules – for Primary Analysis

Study Disposition	FP Collection (FPRR)	Observed MBL Volume	Reason for No FP Collection	Responder Status
Discontinued early due to lack of	N/A	N/A	N/A	Non-responder

efficacy or for surgical intervention for uterine fibroids				
Completed study or discontinued early for other reasons	100% FP Compliance	N/A	N/A	Responder based on the observed MBL volume
	<100% FP Compliance	MBL volume ≥ 80 mL or <50% reduction from Baseline	N/A	Non-responder based on the observed MBL volume
		MBL volume < 80 mL and ≥ 50% reduction from Baseline	N/A	**Based on LOCF MBL volume**
	No FP Collection	N/A	Reported "Amenorrhea"[a]	Responder
			Reported "Spotting or negligible bleeding" confirmed by Diary[b]	Responder
			Reported "Amenorrhea" or "Spotting or negligible bleeding" which was not confirmed, or other reason for no FP collection	**Based on LOCF MBL volume**

Abbreviations: FP, feminine product; EOT, end of treatment; MBL, menstrual blood loss; N/A, not available.
[a] Amenorrhea confirmed if Week 52/EOT visit interval is ≥ 35 days, if amenorrhea reported at prior visit, or if paper diary confirms no bleeding/spotting with use of feminine product for a total of 35 days.
[b] Defined as those patients who meet the following criteria: Diary entry rate > 70% and no more than 3 consecutive days and no more than 5 total days of bleeding/spotting and use of feminine product reported on the Diary over the Week 52/EOT visit window (see Table 7).

7.2.5. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint will be performed to assess whether response rate is consistent across clinically important subgroups. The response rate and 95% CI may be displayed in a separate forest plot for each subgroup. Subgroups will include, but will not be limited to, the subgroups outlined in Table 10.

Table 10: Planned Subgroup Analyses

Subgroup Name	**Subgroup Level**
Geographic region	North America vs Rest of World

Menstrual blood loss volume at Baseline (mL)	< 225 vs ≥ 225 < 120, 120 to < 160, 160 to < 225, ≥ 225
Age category (years)	< 40 vs ≥ 40 < 35, 35 to < 40, 40 to < 45, ≥ 45
Race	Black or African American vs Not Black or African American; Black or African American, White, Other
Volume of myoma at Baseline (cm^3)	< 25 vs ≥ 25
Volume of uterus at Baseline (cm^3)	< 300 vs ≥ 300
BMI (kg/m^2) at Baseline	< 30 vs ≥ 30 < 25, 25 to < 30, 30 to < 35, 35 to <40, ≥ 40
Maximum NRS score for uterine fibroid–associated pain at Baseline	< 4 vs ≥ 4
History of prior pregnancy	Yes/No
Alcohol Use	None, Moderate, Heavy
Smoking History	Never Smoker, Former Smoker, Current Smoker

Abbreviations: BMI = body mass index; NRS = Numerical Rating Scale.

7.3. Secondary Efficacy Endpoints

All efficacy and safety measures over the course of both the parent and extension studies will be presented by the parent study treatment group using descriptive statistics. No treatment comparisons will be performed for this extension study.

7.3.1. Percent Change from Baseline to Week 52 in MBL Volume

The percent change in MBL volume from baseline will be summarized descriptively at each visit. The LS means and 95% CI will be derived using a mixed-effects model with repeated measures and presented as describe in Section 7.1.2. Observed MBL volume for each timepoint will be used, regardless of FPRR. No imputations will be made for missing values.

7.3.2. Proportion of Women Who Achieve Amenorrhea Over the Last 35 Days of Treatment

7.3.2.1. Determination of Amenorrhea

Rules for determining amenorrhea in the treatment period is defined as those who meet 1 of the following requirements for 2 consecutive visits (approximately 56 consecutive days). Patients will be deemed to have amenorrhea during a visit window according to the following rules:

- No feminine product returned due to reported amenorrhea in 2 consecutive visits

OR

- No feminine product returned due to other reasons or feminine product collection with a negligible observed MBL volume coupled with other data indicating infrequent non-cyclic bleeding/spotting as described in Table 11.

Missing responses for menstrual bleeding questions in the paper Diary will be treated as "No Bleeding" if paper Diary compliance rate is > 70%.

Table 11: Rules for Determining Amenorrhea by Visit

Feminine Product Collection (KCAS) [a]	**Patient's Paper Diary**
No feminine product collection due to reported amenorrhea	N/A
No feminine product collection due to other reasons	• Data indicating infrequent, non-cyclic bleeding/spotting defined as bleeding/spotting with feminine product use for no more than 3 consecutive days and no more than 5 days bleeding total per visit window • Diary entry rate > 70%
Feminine product collection with negligible observed MBL volume defined as <5 mL	• Data indicating infrequent, non-cyclic bleeding/spotting defined as bleeding/spotting with feminine product use for no more than 3 consecutive days and no more than 5 days bleeding total per visit window • Diary entry rate > 70%

Abbreviations: eCRF, electronic case report form; MBL, menstrual blood loss; N/A = not applicable.
[a] There is no requirement for feminine product return rate, as the determination of amenorrhea is based on the Diary response.

Patients with amenorrhea over the last 35 days of treatment are defined as those who meet the definition of amenorrhea. If a patient does not return for her Week 52/EOT visit, the paper Diary responses for the last 35 days of treatment will be evaluated, if available. If the criteria for infrequent, non-cyclic bleeding or spotting as indicated in Table 11 is met and the criteria for amenorrhea is met at the prior visit, the patient will be categorized as amenorrheic at Week 52/EOT.

Patients missing amenorrhea reporting for all visits in the extension study will carry forward their Week 24/EOT amenorrhea status from the parent study as their Week 52/EOT amenorrhea status.

7.3.3. Change from Baseline in Hemoglobin

The change in hemoglobin throughout the extension study is evaluated in two subsets of patients. Women with hemoglobin < 11.6 g/dL at baseline meet the definition for below the lower limit of normal. Women with hemoglobin ≤ 10.5 g/dL at baseline meet the criteria for anemia.

The change from baseline and percent change from baseline in hemoglobin will be summarized for each scheduled visit as described in Section 7.1.2. The analysis will be restricted to women with values ≤ 10.5 g/dL at baseline.

The proportion of with an increase in hemoglobin of > 2 g/dL will be summarized for women with hemoglobin values ≤ 10.5 g/dL at baseline. The proportion of with an increase in hemoglobin of ≥ 1 g/dL at Week 52 will be summarized for women with hemoglobin values < 11.6 g/dL at baseline.

7.3.4. UFS-QoL Score

The change from baseline in the UFS-QoL Bleeding and Pelvic Discomfort (BPD) Scale score, UFS-QoL Symptom Severity Scale score, UFS-QoL Revised Activities Scale, UFS-QoL subscale scores, and total scores will be summarized as specified in Section 7.1.2. In addition, the proportion of responders as measured by the BPD Scale score and Revised Activities Scale will be summarized, as described below.

Calculation of UFS-QoL Symptom Severity Scale Score

To calculate the Symptom Severity Scale score, a summed score is created for the items listed below and then the formula below the table is used to transform raw scores to a normalized score with a range of possible values from 0 to 100. This provides Symptom Severity Scale scores, where higher scores are indicative of greater symptom severity and lower scores indicate lower symptom severity.

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Symptom Severity	Sum 1 – 8	8, 40	32

Formula for Transformation of Symptom Severity Raw Scores ONLY:

Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100

Calculation of UFS-QoL Bleeding and Pelvic Discomfort Scale Score

The UFS-QoL BPD Scale has been derived from the UFS-QoL Symptoms Scale; the derivation and validation of this new scale can be found in the MVT-601-3001/3002 SAP. The new scale consists of the following three symptoms proximal to uterine fibroids:

- Heavy bleeding during your menstrual period (Q1)
- Passing blood clots during your menstrual period (Q2)
- Feeling tightness or pressure in your pelvic area (Q5)

To calculate the score for the BPD Scale, a summed score of the items listed below is created and then the formula below the table is used to transform the raw score to a normalized score. This provides BPD Scale scores, where higher score values are indicative of greater symptom severity and lower scores will indicate minimal symptom severity (high scores = bad).

Sub-Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Q1, Q2 and Q5	Sum 1,2,5	3, 15	12

Formula for Transformation of BPD Raw Scores ONLY:

Transformed Score = [(Actual raw score – lowest possible raw score)/(Possible raw score range)] * 100

On the basis of transformed score for BPD Scale, change from Baseline in the transformed score for BPD Scale at Week 52 will be defined as a secondary endpoint. The proportion of patients who are responders (defined as meeting a meaningful change threshold from Baseline in the BPD Scale) at Week 52 on the transformed score for the BPD Scale will be summarized for each treatment group. The proposed responder threshold is a 20-point change. Details in the determination of the meaningful change in the BPD Scale can be found in the MVT-601-3001/3002 SAP Appendix 4.

As a descriptive assessment on robustness of the responder analysis, a plot of the cumulative distribution function (CDF) will be provided for each treatment group to display the change from Baseline to Week 52 in the transformed score for BPD Scale on the x-axis and cumulative percentage of patients experiencing up to that change on the y-axis.

Calculation of Other UFS-QoL Scale Scores and UFS-QoL Total Score

For the other UFS-QoL scales (concern, activities, revised activities, energy/mood, control, self-conscious, and sexual function), a summed score of the items listed below is created for each individual scale. To calculate the UFS-QoL total score, the values for each individual scale are summed. Using the formula below the table, all raw scores are transformed to normalized scores. Higher scores are indicative of better health-related quality of life (high = good).

For endpoints evaluating a single question, the raw score is used in the analysis. The activity and revised activity domain scores will be summarized by treatment group.

Scale	Sum Item Values	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Concern	9+15+22+28+32	5, 25	20
Activities	10+11+13+19+20+27+29	7, 35	28
Revised activities	11+13+19+20+27	5,25	20
Energy/mood	12+17+23+24+25+31+35	7, 35	28
Control	14+16+26+30+34	5, 25	20
Self-conscious	18+21+33	3, 15	12
Sexual function	36+37	2, 10	8
HRQL TOTAL	Sum of 6 Subscale Scores[a]	29, 145	116

Abbreviations: HRQL, health-related quality of life.

[a] HRQL Total includes following scales: concern, activities, energy/mood, control, self-conscious, and sexual function.

Formula for Transformation of Raw Scores of Other Scale Scores ONLY:

$$\text{Transformed Score} = [(\text{Highest possible score} - \text{Actual raw score})/(\text{Possible raw score range})] * 100$$

For revised activities, the proportion of patients who are responders (defined as meeting a meaningful change from Baseline in the revised activity score) at Week 52 will be analyzed similarly to that for the change in BPD Scale score for each treatment group. The proposed responder threshold is a 20-point increase. Details of the determination of the meaningful change in the Revised Activities Scale score can be found in the MVT-601-3001/3002 SAP Appendix 5.

Missing Items

For any scale analyses, if < 50% of the scale items are missing, the scale should be retained using the mean scale score of the items present. If ≥ 50% of the items are missing, no scale score should be calculated; the subscale score will be considered missing.

7.3.5. Change from Baseline to Week 52 in Uterine Volume and Uterine Fibroid Volume

For evaluating percent change from Baseline in uterine fibroid volume and uterine volume that are measured at Week 52, an analysis of covariance (ANCOVA) model will be used to calculate LS means and 95% CI, with randomization stratification factors and Baseline value as covariates. This model will be run separately for each treatment group.

7.3.6. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire results at each visit will be displayed in a by-patient listing.

7.4. Exploratory Efficacy Endpoints

The following exploratory endpoints will be assessed:

- Change from Baseline to Week 52 in the EQ-5D-5L Scale score
- Change from Baseline to Week 52 in EQ-5D-5L visual analogue score (VAS).

7.4.1. Exploratory Efficacy Analyses

The score for each dimension of the EQ-5D-5L Scale (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) will be summarized by visit (baseline, Week 24, Week 52). The change from baseline at Week 24 and Week 52 will be summarized by amount of improvement (1-4 categories), amount of deterioration (1-4 categories), or no change. The VAS will be summarized at each visit and the change from baseline will be summarized at Week 24 and 52 as specified previously for continuous endpoints.

8. PHARMACODYNAMIC ANALYSES

Serum pharmacodynamic data for the extension study consists of serum E2 trough concentrations. This data will be listed and summarized using descriptive statistics (including raw and change from Baseline) by parent study treatment group, and visit. The number and percentage of patients with individual E2 concentration values < 10 pg/mL, 10 to < 20 pg/mL, 20 to < 50 pg/mL, 50 to < 70 pg/mL and ≥ 70 pg/mL will be summarized by parent study treatment group and visit. E2 concentration values below the limit of quantification will be set to half of the lower limit of quantification. Boxplots of E2 concentration values over time, including visits in both the parent study and extension study, will be plotted.

9. SAFETY ANALYSES

Unless otherwise specified, safety analyses will be conducted using the Extension Safety population according to the actual treatment received by the patients in the parent study.

9.1. Adverse Events

Adverse events will be collected from the time of the first dose of open-label study drug through the safety follow up visit approximately 30 days after the last dose of open-label study drug (the end of extension treatment period), or the date of initiation of another investigational agent or hormonal therapy or surgical intervention or entering the MVT-601-035 study, whichever occurs first. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to study drug.

The severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term and system organ class using MedDRA 22.0 or higher.

A treatment-emergent adverse event is defined as any adverse event that occurs after administration of the first dose of parent study drug.

Adverse event summaries will be based on treatment-emergent adverse events in the parent and extension studies, unless otherwise specified. All adverse events in the parent and extension studies will be listed in by-patient listings.

The following tabular summaries that include the number and percentage of patients will be provided:

- Overview of adverse events;
- All adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;
  - Study drug-related per investigator by SOC and PT;
  - By time to onset, SOC and PT;
- Grade 3 or above adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - Study drug-related per investigator by SOC and PT;
- Grade 2 or above adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;

  - Study drug-related per investigator by SOC and PT;
- Adverse events leading to study drug withdrawal;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events leading to dose interruption;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events resulting in fatal outcome;
  - By decreasing frequency of PT;
- Serious adverse events;
  - By SOC and PT;
  - By decreasing frequency of PT;
  - By SOC, PT, and maximum severity;
  - By SOC, PT, and relationship to study drug;
- Adverse events of clinical interest (ALT or AST $\geq 3 \times$ ULN);
  - By SOC, PT, and maximum severity;
  - By decreasing frequency of PT.
- Adverse events with first onset during the extension study;
  - By SOC and PT;
  - By decreasing frequency of PT;

Additionally, adverse event categories defined in Table 12 will be summarized by decreasing frequency of PT.

9.1.1. Relationship to Study Drug

Adverse events will be classified as "related" to study treatment if the relationship was rated by the investigator as possibly related or probably related. Adverse events related to any study drug component (relugolix or placebo and E2/NETA or placebo) will be considered as related to study drug.

9.1.2. Severity of Adverse Event

Grade 2 or higher adverse events will be summarized by SOC, PT, and/or maximum severity, relationship to study treatment.

9.1.3. Serious Adverse Event

Serious adverse events throughout the parent and extension studies will be summarized by SOC, PT, and/or maximum severity, relationship to study treatment.

The data handling conventions for and the definition of a serious adverse event are discussed in this section. All deaths during the studies, including the post treatment follow-up period, and deaths that resulted from a process that began during the studies, should be included in the analysis. For more details, deaths occurring during the following time periods or under the following conditions should be considered:

- Deaths occurring during participation in either the parent study or study MVT-601-3003;
- Deaths occurring after a patient leaves a study, or otherwise discontinues study drug, whether or not the patient completes the study to the nominal endpoint, if the death:
  - Is the result of a process initiated during the study or other drug exposure, regardless of when it actually occurs; or
  - Occurs within a time period that might reflect drug toxicity for a patient leaving a study or otherwise discontinuing drug.

9.1.4. Adverse Event Leading to Withdrawal of Study Drug

Adverse events leading to withdrawal of study drug are those adverse events collected from the adverse event electronic case report form (eCRF) pages with “drug withdrawn” as the action taken with study drug.

Adverse events with “drug withdrawn” as action taken due to any one of the components of study drug will be considered as leading to withdrawal of study drug.

9.1.5. Adverse Events Leading to Dose Interruption

Adverse events leading to dose interruption are those adverse events collected from the adverse event eCRF pages with “drug interrupted” as their action taken with study drug.

Adverse events with “drug interrupted” as action taken due to any one of the components of study drug will be considered as leading to dose interruption.

9.1.6. Adverse Events Resulting to Fatal Outcome

Adverse events resulting in a fatal outcome are those adverse events collected from the adverse event pages with “fatal” as their outcome.

The fatal events, if any, will be provided in a by-subject listing.

9.1.7. Adverse Event Categories

In addition, adverse event categories defined in Table 12 will be summarized by decreasing frequency of PT under each safety population.

Table 12: Constitution of Adverse Event Categories

Category	Search Criteria
Bone health events	Osteoporosis/Osteopenia SMQ (broad) Fracture (custom SMQ): All preferred terms including the term "fracture," excluding "Tooth fracture" and "Fracture of penis"
Hepatic transaminase elevations	Drug-related hepatic disorders – comprehensive SMQ (narrow)
Carbohydrate and lipid metabolic effects	Dyslipidemia SMQ (broad) Hyperglycemia/new onset diabetes mellitus SMQ (narrow)
Vasomotor symptoms	The following five Preferred Terms will be included: Hyperhidrosis; Feeling hot; Hot flush; Night sweats; Flushing.
Mood disorders	MedDRA Depression and Suicide/Self-Injury SMQ (broad)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query.

9.1.8. Exposure-adjusted Adverse Events

Adverse events by time to onset and an exposure-adjusted adverse event analysis will be provided. The exposure-adjusted adverse event rate will be summarized by system organ class and preferred term for each parent study treatment group, where the exposure-adjusted adverse event rate is calculated as number of patients with a particular adverse event by total exposure-time among patients at risk of an initial occurrence of the event. Exposure-time is derived as exposure to any study drug throughout the parent and extension study.

9.2. Laboratory Data

Laboratory parameters, including chemistry and hematology panels, specified as per protocol for the parent and extension studies, and collected from the central laboratory will be tabulated and presented in by-patient listings. Urinalysis and hepatitis virus serological test results will be provided in by-patient listing only.

The National Cancer Institute CTCAE Grading Scale with numeric component will be used to categorize toxicity grade for laboratory parameters (CTCAE v5.0, dated 27 Nov 2017). Parameters that have criteria available for both low and high values (eg, hypercalcemia for a high value of calcium and hypocalcemia for a low value of calcium) will be summarized for both criteria (low and high). Patients will only be counted once for each criterion. The same patient can be counted for both criteria if she has laboratory values meeting each criterion. Shift tables will be provided for each gradable parameter to summarize Baseline toxicity grade versus worst post-Baseline toxicity grade throughout the parent and extension studies. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low,

normal, and high) will be provided for each parameter to summarize the Baseline versus worst post-Baseline results throughout the parent and extension studies.

Boxplots of laboratory values over time, including visits in both the parent study and extension study, will be plotted for key laboratory parameters. These laboratory parameters include, but are not limited to, hematology (hemoglobin, platelets, leukocytes, neutrophils), creatinine, glomerular filtration rate, and hepatic function panel (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin).

The change from Baseline to each post-Baseline study visit will be presented by parent study treatment group for each laboratory test in both tables and figures.

The number and proportion of patients with liver test elevations will be presented by parent study treatment group. Liver test elevations are assessed by using post-Baseline results for ALT, AST, ALP, and total bilirubin based on the definitions presented in Table 13.

Table 13: Categories of Liver Test Elevations

Laboratory Test	Category
ALT or AST	ALT or AST > ULN < 3 × ULN ALT or AST ≥ 3 × to < 5 × ULN ALT or AST ≥ 5 × to < 10 × ULN ALT or AST ≥ 10 to < 20 × ULN ALT or AST ≥ 20 × ULN
Total bilirubin	Total bilirubin > 2 × ULN
ALT or AST and total bilirubin	ALT or AST ≥ 3 × ULN + total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	ALT or AST ≥ 3 x ULN + total bilirubin > 2 × ULN + ALP < 2 × ULN

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.

The number and percentage of patients with concurrent (defined as measurements on the same day) ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN will also be presented.

Selected chemistry and hematology test results meeting pre-defined limits of change at any time and based on last observation on treatment will be also summarized per pre-defined threshold (refer to Appendix 1) by parent study treatment group.

9.3. Other Safety Analyses

9.3.1. Electrocardiograms

ECG interval results and changes from Baseline will be summarized descriptively for each scheduled visit, including visits in both the parent study and extension study, in both tables and figures using data provided by and read by central reading.

A categorical analysis of corrected QT interval using Fridericia's calculation (QTcF) intervals will also be performed for each scheduled visit and for the maximum post-Baseline value. The

number and percentage of patients in each QTcF interval category (< 450 msec, 450 to 480 msec, 481 to 500 msec, and > 500 msec) will be summarized. Categories of changes from Baseline (≥ 30 msec and ≥ 60 msec) will be summarized as well.

ECG intervals will be presented in by-patient listing. Overall ECG assessments performed by local reading will also be listed.

9.3.2. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and BMI will be summarized at Baseline and each subsequent scheduled assessment, including visits in both the parent study and extension study, by parent study treatment group. Change from Baseline will be calculated and presented for each parameter at all scheduled post-Baseline assessment time points in both tables and figures. All vital sign data will also be provided in by-patient listings.

Potentially clinically significant abnormalities in vital signs are defined in Table 14, and they will be summarized by using post-Baseline values that meet the defined criteria. Potentially clinically significant abnormalities will also be flagged in by-patient listings.

Table 14: Categories of Potentially Clinically Significant Abnormalities in Vital Signs

Parameter	Category
Systolic blood pressure	≥ 140 mmHg ≥ 180 mmHg
	≤ 90 mmHg
	Increase of ≥ 20 mmHg from Baseline Decrease of ≥ 20 mmHg from Baseline
Diastolic blood pressure	≥ 90 mmHg ≥ 105 mmHg
	≤ 50 mmHg
	Increase of ≥ 15 mmHg from Baseline Decrease of ≥ 15 mmHg from Baseline
Heart rate	≥ 120 bpm
	< 45 bpm
	Increase of ≥ 15 bpm from Baseline Decrease of ≥ 15 bpm from Baseline

Abbreviations: bpm = beats per minute; mmHg = millimeters of mercury.

9.3.3. Endometrial Biopsy

The protocol-specified endometrial biopsy procedure is performed at the Week 52 or Early Termination Visit in the extension study. Consensus readings were performed on all endometrial biopsies. Endometrial biopsies will be summarized according to primary diagnosis categories

from the consensus reading (Table 15). Endometrial biopsies performed in the parent studies and in the extension study at Week 52 or at the time of early termination will be summarized. Any repeat endometrial biopsies performed will also be summarized. All endometrial biopsy data will also be provided in a by-patient listing, including visits in both the parent study and extension study.

Table 15: Categories of Primary Diagnosis in Endometrial Biopsies

Category	Diagnosis
Atrophy/Inactive	• Limited surface endometrium • Atrophy • Inactive
Proliferative	• Weakly proliferative • Active proliferative • Disordered proliferative pattern
Mixed	• Mixed proliferative and secretory
Secretory/Menstrual	• Secretory cyclic type • Secretory progestational type (including stromal decidualization) • Non secretory endometrium with breakdown • Menstrual
Reactive/Inflammatory	• Chronic Endometritis • Acute Endometritis
Polyp	• Polyp, atrophic • Polyp, functional • Polyp, hyperplastic • Polyp, adenomyomatous • Polyp, other
Hyperplasia	• Hyperplasia, simple, without atypia • Hyperplasia, complex, without atypia • Hyperplasia, simple, with atypia • Hyperplasia, complex, with atypia
Carcinoma	• Malignant carcinoma • Malignant sarcoma • Malignant mixed Mullerian tumor • Malignant, other
Other	• Benign tumor • Other non-physiologic epithelial changes

Other: cannot classify based on provided information	—
Inadequate	• No specimen in container: verified by pathologist • Tissue unsatisfactory for diagnosis: no endometrium present • Tissue unsatisfactory for diagnosis: too scant for reliable diagnosis

9.3.4. Bone Mineral Density

Corrected BMD data will be used for analysis as determined by the central radiology laboratory in the three prespecified anatomical locations: lumbar spine (L1–L4), total hip, and femoral neck.

BMD measured at Baseline, Week 12, Week 24, Week 36, and Week 52 visits will be summarized descriptively by parent study treatment group and each measured anatomical location for all patients in the Extension Safety population. Percentage changes from baseline along with 95% CIs of mean percentage changes also will be summarized by parent study treatment group and anatomical location. Mean percentage change from baseline with its corresponding 95% CI will be plotted by visit, parent study treatment group, and anatomical location.

A mixed-effects model with repeated measures will be used to assess BMD at 12, 24, 36, and 52 weeks. The model will be generated separately for each parent study treatment group and will have age at Baseline, visit, Baseline BMD value, stratification factors (geographic region and menstrual blood loss volume [as entered in the interactive web response system at the time of randomization]), race (African American versus Other), and BMI at Baseline as fixed effects using an unstructured variance-covariance matrix. Least square means on each anatomical location will be presented and plotted at each visit with associated 95% CIs. Categorical representation of percentage change from Baseline to 12, 24, 36, and 52 weeks of treatment will be presented by the number and proportion of patients who had BMD declines of ≤ 2%, >2% to 3%, > 3% to 5%, > 5% to 8%, and > 8% by parent study treatment group and anatomical location. The 95% CIs will be provided for the respective proportions.

Categorical changes from Baseline in overall BMD (defined as lumbar spine and total hip) also will be assessed at 12, 24, 36, and 52 weeks. Femoral neck evaluates a smaller area of bone mass than the total hip and is prone to lower precision in the measurement (Leslie 2007; ISCD Official Positions 2015). Since femoral neck BMD may be associated with discordant readings compared with the total hip or lumbar spine due to technical considerations, it is not expected to add meaningful interpretation of overall BMD changes in response to treatment, though will be included for completeness.

Z-scores will be summarized by parent study treatment group, visit, and anatomical location with descriptive statistics including 95% CIs, and the number and percentage of patients with a Z-score < -2.0 will be presented by parent study treatment group, visit, and anatomical location.

BMD percentage changes from Baseline will also be summarized by intrinsic factors (eg, age, race, body mass index) and extrinsic factors (eg, geographic region). Subgroups will include, but will not be limited to, the subgroups outlined in Table 16.

Table 16: Planned Subgroup Analyses

Subgroup Name	Subgroup Level
Geographic region	North America, Rest of World
Age category (years)	< 40, ≥ 40
Race	Black or African American, Not Black or African American
Ethnicity	Hispanic or Latino, Not Hispanic or Latino
BMI (kg/m^2) at Baseline	<30, ≥ 30

Abbreviations: BMI = body mass index.

Patients not enrolling in the MVT-601-035 study who had evidence of BMD loss of > 3% at the lumbar spine (L1 to L4) or total hip at their Week 52/EOT visit relative to the pre-treatment baseline measurement and patients who has evidence of BMD loss of > 2% at the lumbar spine (L1 to L4) or total hip at their EOT occurring prior to Week 36, underwent further testing and follow-up to evaluate recovery per the protocol. All available 6-month and 12-month post-treatment follow-up BMD data will be summarized to display the number and percent of patients who completed post-treatment follow-up, who met the threshold for recovery, and who did not meet the threshold for recovery.

10. REFERENCES

2015 International Society for Clinical Densitometry (ISCD) Official Positions – Adult (https://www.iscd.org/official-positions/2015-iscd-official-positions-adult/; accessed 30 Apr 2019).

Leslie WD, Lix LM, Tsang JF, Caetano PA. Single-site vs Multisite Bone Density Measurement for Fracture Prediction. Arch Intern Med 2007; 167 (15): 1641-7

APPENDICES

APPENDIX 1: LIST OF PRE-DEFINED THRESHOLD IN SELECTED CHEMISTRY AND HEMATOLOGY TEST RESULTS

Chemistry Laboratory	
Liver Function	
ALT > ULN and < 3× ULN	Total BILI > ULN
ALT ≥ 3× ULN and < 5× ULN	Total BILI >2× ULN
ALT ≥ 5× ULN and < 10× ULN	
ALT ≥ 10× ULN and < 20× ULN	ALT or AST ≥ 3× ULN and Total BILI > 2× ULN
ALT ≥ 20× ULN	ALT or AST ≥ 3× ULN and Total BILI > 2× ULN and ALP < 2× ULN
AST > ULN and < 3× ULN	GGT > ULN and < 3× ULN
AST ≥ 3× ULN and < 5× ULN	GGT ≥ 3× ULN and < 5× ULN
AST ≥ 5× ULN and < 10× ULN	GGT ≥ 5× ULN and < 10× ULN
AST ≥ 10× ULN and < 20× ULN	GGT ≥ 10× ULN and < 20× ULN
AST ≥ 20× ULN	GGT ≥ 20× ULN
ALT or AST > ULN and < 3× ULN	
ALT or AST ≥ 3× ULN and < 5× ULN	
ALT or AST ≥ 5× ULN and < 10× ULN	
ALT or AST ≥ 10× ULN and < 20× ULN	
ALT or AST ≥ 20× ULN	
Renal Function	
CR > 1.5 mg/dL and > BL	GFR < 15 mL/min per 1.73 m^2
CR > 50% increase from BL	GFR ≥ 15 - < 30 mL/min/1.73 m^2
	GFR ≥ 30 - < 60 mL/min min/1.73 m^2
	GFR ≥ 60 - < 90 mL/min min/1.73 m^2
	GFR ≥ 90 mL/min min/1.73 m^2

Chemistry Laboratory	
Metabolic Parameters	
Fasting Glucose	Highest Postbaseline Glucose
< 100 mg/dL at BL	Gluc ≥ 200 mg/dL and > BL
< 100 mg/dL at Week 24	Gluc ≥ 200 mg/dL and ≥ 126 BL
≥ 100 - < 126 mg/dL at Week 24	Gluc ≥ 500 mg/dL
≥ 126 mg/dL at Week 24	Gluc ≥ 500 mg/dL and ≥ 126 BL
≥ 100 - < 126 mg/dL at BL	Total CHOL > 200 mg/dL and > BL
< 100 mg/dL at Week 24	Total CHOL increase > 30 mg/dL from BL
≥ 100 - < 126 mg/dL at Week 24	
≥ 126 mg/dL at Week 24	HDL < LLN and < BL
	LDL > ULN and > BL
≥ 126 mg/dL at BL	TRIG > ULN and > BL
< 100 mg/dL at Week 24	
≥ 100 - < 126 mg/dL at Week 24	
≥ 126 mg/dL at Week 24	
Electrolytes and other Chemistry Parameters	
ALB < LLN and < BL	CK > 2× ULN and > BL
ALB > ULN and > BL	CK > 5× ULN and > BL
	CK > 10× ULN and > BL
ALP > 2× ULN and > BL	
ALP > 5× ULN and > BL	MG < LLN and < BL
ALP > 10× ULN and > BL	MG > ULN and > BL
CA < LLN and < BL	PHOS < LLN and < BL
CA > ULN and > BL	PHOS > ULN and > BL

K < LLN and < BL	NA < LLN and < BL
K > ULN and > BL	NA > ULN and > BL
Hematology Laboratory	
HCT < LLN and < BL	NEUT < LLN and < BL
HCT decrease ≥ 10 from BL	NEUT > ULN and > BL
HGB ≤= 10.5 g/dL and < BL	BASO < LLN and < BL
HGB decrease > 1 g/dL from BL	BASO > ULN and > BL
MCV < LLN and < BL	EOS < LLN and < BL
MCV > ULN and > BL	EOS > ULN and > BL
	EOS > 5% and > BL
WBC < LLN and < BL	
WBC > ULN and > BL	PLT < LLN and < BL
	PLT < 100 × 10^9/L and < BL
LYM < LLN and < BL	PLT > ULN and > BL
LYM > ULN and > BL	
	HbA1c ≥ 6.5 and > BL
MONO < LLN and < BL	HbA1c increase > 1.0 from BL
MONO > ULN and > BL	

Abbreviations: ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase ; BL = baseline; BILI = bilirubin; CA = calcium; CHOL = cholesterol; CR = creatinine; EOS = eosinophils; GGT = gamma-glutamyl transferase; HCT = hematocrit; HDL = high-density lipoprotein; HbA1c = hemoglobin A1C; HGB = hemoglobin; K = potassium; LDL = low-density lipoprotein; LLN = lower limit of normal; LYM = lymphocytes; MG = magnesium; MCV = mean corpuscular volume; MONO = monocytes; NA = sodium; PHOS = phosphorus; PLT = platelets; ULN = upper limit of normal; WBC = while blood cells.