STATISTICAL ANALYSIS PLAN

Study Titles:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	IND # 076642 EudraCT # 2017-004066-10
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STATISTICAL ANALYSIS PLAN APPROVAL SHEET

SPIRIT 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 Endometriosis-Associated Pain

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

PPD

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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
bpm	beats per minute
CI	confidence interval
CR	creatinine
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
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ET	early termination
EHP	Endometriosis Health Profile
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
ICH	International Council on Harmonisation
LS	least squares
MAA	Marketing Authorization Application
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
msec	millisecond
NETA	norethindrone acetate
NDA	New drug application
NMPP	non-menstrual pelvic pain
NRS	Numerical Rating Scale
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PT	Preferred Term
QTcF	corrected QT interval Fridericia
SAP	statistical analysis plan
sB&B	Subject Modified Biberoglu and Behrman
SD	standard deviation
SMQ	standard MedDRA query

Term	Definition/Explanation
SOC	System Organ Class
ULN	upper limit of normal
LLN	lower limit of normal
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-601-3103, 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 Endometriosis-Associated Pain." Patients who completed study MVT-601-3101 (SPIRIT 1) or study MVT-601-3102 (SPIRIT 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-601-3103.

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

This SAP is based on:

- Protocol MVT-601-3103, Amendment 4, dated 1 Jul 2021;
- ICH guidelines E3 (Clinical Study Reports) and E9 (Statistical Principles for Clinical Trials).

The methods used for analysis of the MVT-601-3103 study are consistent with those used for the pivotal phase 3 studies (MVT-601-3101 and MVT-601-3102). This document may evolve over time (eg, to reflect the requirements of protocol amendments or regulatory requests). The SAP is to be finalized, approved by the sponsor, and placed on file before the database is locked for the final clinical study report (CSR). The final SAP may be amended prior to the database lock for the final CSR.

1.1. Study Objectives and Endpoints

The objectives of study MVT-601-3103 are to evaluate long-term efficacy and safety through up to 104-week of treatment (including 24 weeks of treatment during the pivotal phase 3 studies) of relugolix 40 mg once daily co-administered with estradiol and norethindrone acetate. 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. The pivotal phase 3 study Baseline will be in general used as the reference point for the extension study for all changes from baseline-related endpoints unless otherwise specified.

Table 1: Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Efficacy	
To be assessed at Week 52 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 pivotal phase 3 studies (MVT-601-3101 or MVT601-3102), on endometriosis-associated pain.	To be assessed Week 52 • Proportion of patients who meet the dysmenorrhea responder criteria at the Week 52 pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary • Proportion of patients who meet the NMPP responder criteria at the Week 52 pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary
To be assessed at Week 104 To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	To be assessed at Week 104 • Proportion of patients who meet the dysmenorrhea responder criteria at the Week 104/EOT pain assessment period, achieving a mean reduction in dysmenorrhea NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary • Proportion of patients who meet the NMPP responder criteria at the Week 104/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary
Secondary Efficacy (To be assessed at Week 52 and Week 104, unless otherwise specified)	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and	To be assessed on the following:

Objective(s)	Endpoint(s)
norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT601-3102), on the following:	
○ Function, as measured by the Endometriosis Health Profile Questionnaire (EHP-30) Pain Domain	Change from the pivotal phase 3 study Baseline in the EHP-30 Pain Domain scores; Proportion of patients who have a reduction of at least 20 points in the EHP-30 Pain Domain scores from the pivotal phase 3 study Baseline
○ Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea	Change *and percent change* from the pivotal phase 3 study Baseline in the mean dysmenorrhea NRS score
○ Patient Global Impression of Change (PGIC) for dysmenorrhea	Proportion of patients who are "better" or "much better" on the PGIC for dysmenorrhea (at Week 52 only)
○ Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP	Change *and percent change* from the pivotal phase 3 study Baseline in the mean NMPP NRS score
○ Overall pelvic pain, as measured by the NRS for overall pelvic pain	Change *and percent change* from the pivotal phase 3 study Baseline in the mean overall pelvic pain NRS score
○ Analgesic use	*Proportion of patients not using opioids;* *Proportion of patients not using analgesics*
○ PGIC for NMPP	Proportion of patients who are "better" or "much better" on the PGIC for NMPP (at Week 52 only)
○ Dyspareunia, as measured by the NRS	Change *and percent change* from the pivotal phase 3 study Baseline in the mean dyspareunia NRS scores
○ PGIC for dyspareunia	Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only)

Objective(s)	Endpoint(s)
○ Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B])	Change *and percent change* from the pivotal phase 3 study Baseline in the mean dyspareunia functional impairment on the sB&B scale
○ Patient Global Assessment (PGA) for pain	Change from the pivotal phase 3 study Baseline in severity scores on the PGA for pain; *Proportion of Patients with Improvement, Worsening, No change from baseline;*
○ PGA for function	Change from the pivotal phase 3 study Baseline in function impairment on the PGA for function; *Proportion of Patients with Improvement, Worsening, No Change from Baseline*
○ Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains	Change from the pivotal phase 3 study in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image)
○ Dysmenorrhea-related functional effects (sB&B)	Change *and percent change* from the pivotal phase 3 study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B)
○ NMPP-related functional effects (sB&B)	Change *and percent change* from the pivotal phase 3 study Baseline pain assessment period in NMPP-related functional effects (sB&B)

Objective(s)	Endpoint(s)
Safety	
• To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102), including: o Adverse events o Changes in bone mineral density	To be assessed at Week 52 and Week 104 • Incidence of adverse events • Percent change from the pivotal phase 3 study Baseline to Week 52 or Week 104 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA) To be assessed at 6-months and 12-months post-treatment • Percent change from the parent study Baseline in BMD at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by 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 104 weeks, among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT601-3102), on estradiol	• Change from pivotal phase 3 study Baseline to Week 52 in pre-dose concentrations of serum estradiol • Change from pivotal phase 3 study Baseline to Week 104 in pre-dose concentrations of serum estradiol
Exploratory Efficacy	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102)	To be assessed at Week 52 and Week 104 • Change from pivotal phase 3 study Baseline in the EHP-30 scale total score • Change from pivotal phase 3 study Baseline in the EHP Work Domain score. • Change from pivotal phase 3 study Baseline in the EQ-5D-5L

Descriptive assessments of efficacy and safety will be made on data collected from the pivotal phase 3 study Baseline through Week 52, and from the pivotal phase 3 study Baseline through the end of the extension study (Week 104) on the extension study population, defined as patients who enrolled in MVT-601-3103 (i.e., who received at least one dose of study drug in the extension study), for the following treatment groups originally randomized in the pivotal phase 3 studies:

- Pivotal phase 3 relugolix + E2/NETA group: 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 pivotal phase 3 study;
- Pivotal phase 3 relugolix + delayed E2/NETA group: 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 pivotal phase 3 study;
- Pivotal phase 3 placebo group: Randomized to 24 weeks to placebo in the pivotal phase 3 study.

2. STUDY DESIGN

2.1. Summary of Study Design

The SPIRIT 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 randomized, double-blind, placebo-controlled pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102). All patients will receive oral relugolix 40 mg once daily co-administered with estradiol 1 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Patients will continue to be followed up for their BMD for 12 months after their treatment period has ended.

Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment during the pivotal phase 3 study) which will include up to 80 weeks of treatment with relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102) and consented to participate in this extension study.

Baseline procedures will be done at the same visit (referred to as the "Week 24/Baseline visit" in this study), which coincides with the Week 24 visit from the pivotal phase 3 study and will be defined as the date of completion of the last Week 24 procedure in the pivotal phase 3 study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the pivotal phase 3 study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients would have received their last dose of study drug in the pivotal phase 3 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. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Patients 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 80 weeks. If necessary, for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the pivotal phase 3 study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the pivotal phase 3 study safety follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment period and the ~30-day Follow-Up period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary during the time periods specified in the protocol. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet, according to the study protocol Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by monitoring adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, mammograms (for women who are or become ≥ 40 years old during the study), endometrial biopsies, and bone mineral density with DXA.

At scheduled visits, Early Termination visit, and post-treatment Follow-Up, each patient will have an assessment of bone mineral density (BMD) by DXA if required by protocol or protocol amendment.

Determination of BMD by DXA at the Early Termination visit, scheduled visits and post-treatment Follow-Up of findings will proceed according to the following rules:

Table 2. BMD Requirement by DXA in Protocol and Amendments

Protocol	Scheduled Visits and Early Termination	Post-Treatment Follow-Up
Original	At week 52 visit, DXA is required. DXA at Early Termination (ET) visit is required, but DXA is not required at the Early Termination visit in patients whose last dose of	Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/ET visit relative to the pivotal phase 3 study Baseline measurement will undergo another bone densitometry scan at 6 (±1) months after the last dose of study medication.

	study drug was taken during Week 32 or earlier. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.	If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-Up visit and the follow-up bone densitometry scan at 6 (±1) months may be waived.
AM1.0	At the Week 36 and Week 52, visits, DXA is required. DXA at ET visit is required, but DXA is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within 4 weeks after completion of the Week 36 scan. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.	Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/ET visit (or most recent scan, if the Week 52/ET scan was not done) relative to the pivotal phase 3 study Baseline measurement will undergo another bone densitometry scan at 6 (±1) months after the last dose of study medication. If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-Up visit and the follow-up bone densitometry scan at 6 (±1) months may be waived.
AM 2.0	At the Week 36, Week 52, and Week 104 visits, DXA is required. • For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event • For Early Termination occurring after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination	Post-Treatment DXA is required at 6 months (± 1 month) for following: • For Early Termination occurring before Week 36: – the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the pivotal phase 3 study baseline. • For Early Termination occurring after Week 36 and before Week 52: – the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the pivotal phase 3 study baseline; or – on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the pivotal phase 3 study baseline. • For Early Termination occurring between Week 52 and Week 104: – on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to pivotal phase 3 study baseline.

		If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-Up visit and the follow-up procedures performed under this protocol, the follow-up bone densitometry scan at 6 (±1) months may be waived.
AM 3.1	At the Week 36, Week 52, and Week 104 visits, DXA is required. • For Early Termination occurring before Week 36, DXA is not required at the Early Termination visit unless it will aid in the assessment of an adverse event or if the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the pivotal phase 3 study baseline. • For Early Termination occurring at or after the Week 36 visit, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.	Post-Treatment DXA is required at 6 months (± 1 month): • For Early Termination occurring before Week 36: – the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the pivotal phase 3 study baseline. • For Early Termination occurring at or after the Week 36 visit: – the most recent DXA scan was at Week 24 and on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the pivotal phase 3 study baseline. – the most recent DXA was after the Week 24 visit and on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the pivotal phase 3 study baseline. • For patients who complete the open-label extension study: – at the Week 104 visit or on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the pivotal phase 3 study baseline. 12-Month Post-Treatment DXA: patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with the pivotal phase 3 study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow

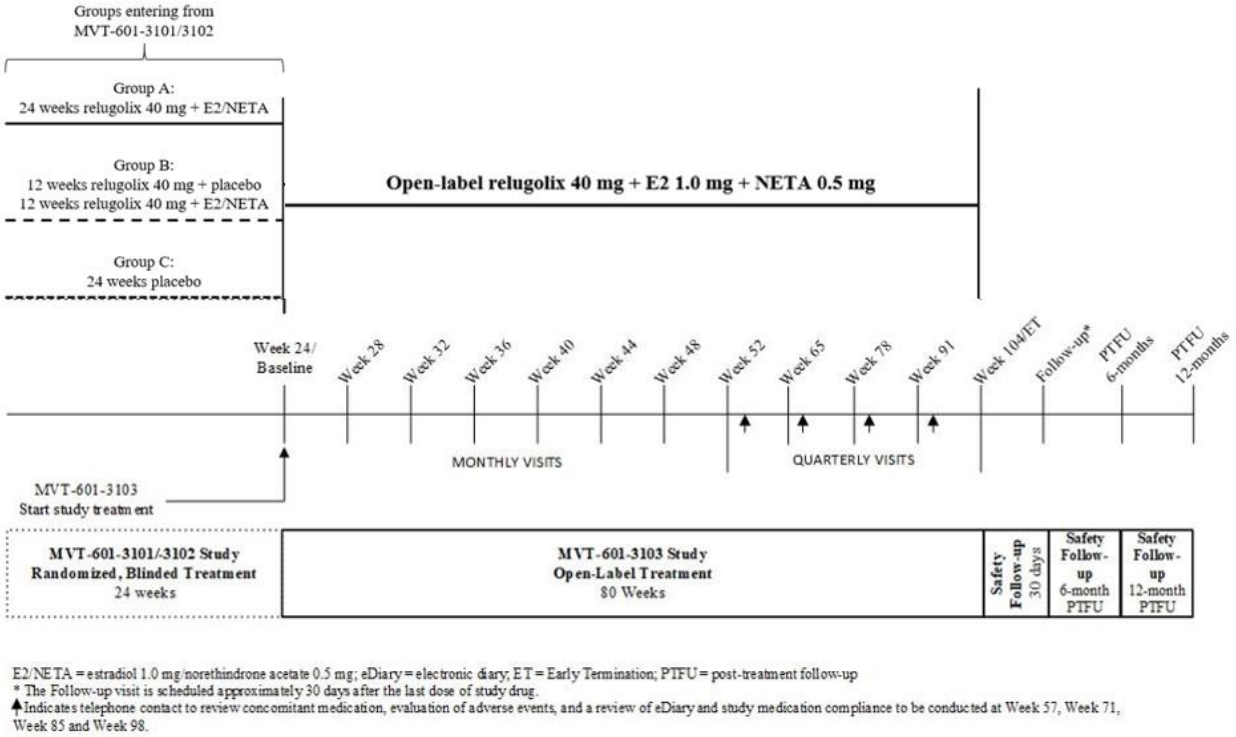
AM 4.0	• For Early Termination occurring before Week 36, DXA is not required at the Early Termination visit unless it will aid in the assessment of an adverse event or if the most recent DXA BMD loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. • For Early Termination occurring at or after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.	6-month and 12-Month Post-Treatment DXA: • All ongoing patients, after they complete the Week 104 visit or terminate the study early, will return for a 6-month PTFU DXA and a 12-month PTFU DXA • All patients who completed treatment or terminated from the study early and are within 6 months from their last day on treatment will be requested to return for a 6month PTFU DXA and again for a 12-month PTFU DXA. • All patients who completed treatment or terminated from the study early and are past 6 months but within 12 months from their last day on treatment will be requested to return for a 12-month post-treatment DXA. • For patients who are outside the PTFU visit windows, PTFU DXA is still recommended. However, if the patient is beyond 14 months from last day on treatment, she does do not need to return for 12-month post-treatment DXA. If patients have 6-month or 12-month PTFU scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with the parent study baseline, patients should be referred to and strongly encouraged to see a bone specialist for further evaluation of the bone loss.

The 6-month and 12-month PTFU visits will also measure post-treatment medical and gynecological history, concomitant medications, and bone fracture events. Patients should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous at the 6-month and 12-month PTFU visit only if PTFU scans show a bone loss of ≥ 3% at the lumbar spine and/or total hip compared with the parent study baseline.

Status of menstruation recovery will be documented at the Safety Follow-Up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted again by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient. A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study

A schematic of the MVT-601-3103 study is presented in Figure 1.

Figure 1 MVT-601-3103 Study Schematic



E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; eDiary = electronic diary; ET = Early Termination; PTFU = post-treatment follow-up
* The Follow-up visit is scheduled approximately 30 days after the last dose of study drug.
▲Indicates telephone contact to review concomitant medication, evaluation of adverse events, and a review of eDiary and study medication compliance to be conducted at Week 57, Week 71, Week 85 and Week 98.

2.2. Sample Size Considerations

It was estimated approximately 800 patients (67% of the total of planned 1200 patients who would be randomized to the pivotal phase 3 studies (MVT-601-3101 or MVT-601-3102) and had completed either study) were eligible and willing to participate in this extension study.

3. PLANNED ANALYSES

The final analysis of the data includes data through Week 104 and all post-treatment follow-up data.

3.1. Final Analyses

The final analyses of all efficacy and safety data from MVT-601-3103 will occur after all enrolled patients have either completed 80 weeks of open-label treatment with relugolix + E2/NETA and the 30-day safety Follow-Up visit or discontinued early from the study. The results of the final analyses will be used for the final CSR for MVT-601-3103.

3.2. Safety Follow-Up Analyses

If the first menstruation after the end of study treatment administration is observed before the Follow-Up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

Bone mineral density by DXA at 6-month and 12-month Post-Treatment will be proceed according to the rules mentioned in Section 2.1 Table 2. The follow-up bone densitometry will be submitted for central reading.

Post-treatment medical and gynecological history, concomitant medications, and bone fracture events will be measured at the 6-month and 12-month PTFU visits. Patients with PTFU scan bone loss ≥ 3% at the lumbar spine and/or total hip compared with the pivotal study baseline will have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.

Data collected during the additional safety Follow-Up period that are available at the time of database lock for final analyses will be summarized and reported in the final 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. Only descriptive analyses will be provided. Formal statistical comparisons are not planned.

All confidence intervals (Cis) will be reported as two-sided 95% Cis 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 pivotal phase 3 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 decimal place, unless otherwise specified. For BMD DXA, mean and median values will be formatted to two decimal places. Standard deviation values will be formatted to two more decimal places, unless otherwise specified. 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 in pivotal phase 3 study. 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 analysis.
- For safety analyses, percentages will be calculated based on the number of patients in the analysis population in each pivotal phase 3 study treatment group.

- For by-visit observed data analyses, percentages will be calculated based on 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, minimum, and maximum.
- For time-to-event endpoints, the summary statistics will include median time to event-free survival, the 25th and 75th percentiles, and the number of patients at risk at specified time points.
- For categorical endpoints, the summary statistics will include counts and percentages;
- Confidence intervals will be constructed at the 95% level. For binomial variables, exact methods will be employed, unless otherwise specified.

4.2. Analysis Populations

The protocol specified efficacy and safety analyses will be performed on the Extension Study Population as defined in Section 4.2.1 and Section 4.2.2, respectively. The Week 52 efficacy analyses will include efficacy data up to 52 weeks of treatment on the Extension Study population. The Week 52 safety analyses will include safety data up to 52 weeks or safety Follow-Up if patients early terminated the study before Week 52 on the Extension Safety population. The final analysis will include efficacy data up to 104 weeks of treatment on the Extension Study Population and safety data up to safety Follow-Up on the Extension Safety population.

4.2.1. Extension Study Population

The Extension Study population is defined as all patients who enrolled into MVT-601-3103 and who have received any amount of open-label study drug in MVT-601-3103. All efficacy analyses will be performed on the Extension Study population, unless otherwise specified. Efficacy analyses will be performed by treatment group as randomized in the pivotal phase 3 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 MVT-601-3103. Any patient who received at least one dose of relugolix will be considered as a relugolix patient for purposes of safety analyses, consistent with analysis in the pivotal phase 3 studies. All safety analyses will be performed on the Extension Safety population, unless otherwise specified. Safety data will be analyzed by pivotal phase 3 study treatment group according to the actual treatment received (not the randomized treatment) in pivotal phase 3 study.

4.2.3. Exclusion of Site PPD from Efficacy and Safety Analyses

Due to the results of an audit which found evidence of data integrity issues at the Site PPD (in study MVT-601-3102), the data of three patients enrolled into the open-label extension study at that site will be excluded from all efficacy and safety analyses. The data for these three patients

will be presented in disposition table and listing, and in listing of patients excluded from efficacy and safety analyses.

4.3. Definitions, Computation, and Convention

4.3.1. Definition of Date of First Dose and Date of Last Dose of Pivotal phase 3 Study Drug

The date of first dose of pivotal phase 3 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-601-3101 or MVT-601-3102. The date of last dose of pivotal phase 3 study drug is defined as the date a patient receives the last dose of study drug in the pivotal Phase 3 study MVT-601-3101 or MVT-601-3102, prior to or on the Week 24 visit date. The exact date of last dose of pivotal phase 3 study drug will be known for all patients entering the MVT-601-3103 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-601-3103 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-601-3103 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 the day of the 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 pivotal phase 3 study (Study Day 1). For assessments conducted on or after the date of the first dose of pivotal phase 3 study drug, study day will be calculated as:

(Assessment date – date of first dose of pivotal phase 3 study drug) + 1

For assessments conducted before the date (and time) of the first dose of pivotal phase 3 study drug, study day will be calculated as:

(Assessment date – date of first dose of pivotal phase 3 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)

4.3.5. Definition of Overall Treatment Duration

In the final analysis, overall treatment duration is defined as the duration of time from the date of the first dose of pivotal phase 3 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 pivotal phase 3 study drug) + 1

For patients missing day and month of the last dose date of extension study drug, the last date extension study drug was dispensed will be used to calculate overall 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

In final analysis, extension study treatment duration 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 extension study 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 pivotal phase 3 study. A post-Baseline value is defined as a measurement taken after the first administration of study drug in the pivotal phase 3 study. 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.

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 3: Visit Windows for Monthly and Quarterly Assessments (Monthly and Quarterly Visit, Lab and PGA) (Monthly and Quarterly Visit, Lab and PGA), Table 4 (BMD), Table 5 (electrocardiogram [ECG]), Table 6 (EHP-30), Table 7 (EHP work domain and EQ-5D-5L), Table 8 (PGIC), Table 9 (Endometriosis Biopsy), Table 10 (Mammogram), and Table 11 (eDairy) 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 pivotal phase 3 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 3: Visit Windows for Monthly and Quarterly Assessments (Monthly and Quarterly Visit, Lab and PGA)

Visit	Start Day	Target Day	End Day
Week 4[a]	1(2[b])	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	411
Week 65	412	456	502
Week 78	503	547	593
Week 91	594	638	684
Week 104	685	731	Date of last dose + 6 days
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] For Patient Global Assessments (PGAs), the start day of the Week 4 visit window begins at Day 2.

[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 endometriosis-associated pain.

Table 4: 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
Week 104	647	731	815
6-month post-treatment Follow-Up	Date of last dose + 150 days	Date of last dose + 180 days	Date of last dose + 304 days
12-month post-treatment Follow-Up	Date of last dose + 305 days	Date of last dose + 365 days	Date of last dose + 425 days

Table 5: Visit Windows for ECG Assessments

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Week 52	309	365	421
Week 104	675	731	787

Table 6: Visit Windows for EHP-30 Questionnaire Assessments

Visit	Start Day	Target Day	End Day
Week 12	64	85	106
Week 24	148	169	196
Week 36	197	253	308
Week 48	309	337	351
Week 52	352	365	421
Week 78	491	547	603
Week 104	675	731	787

Table 7: Visit Windows for EHP Work Domain and EQ-5D-5L Assessments

Visit	Start Day	Target Day	End Day
Week 24	128	169	196
Week 52	309	365	421
Week 78	491	547	603
Week 104	675	731	787

Table 8: Visit Windows for PGIC 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

Table 9: Visit Windows for Endometrial Biopsies Assessments

Visit	Start Day	Target Day	End Day
Week 24	128	169	196
Week 52	309	365	421
Week 104	675	731	787
Safety Follow-Up [a]	Date of last dose + 7 days	Date of last dose + 30 days	Date of last dose + 60 days

[a] 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 endometriosis-associated pain. Assessments after date of last dose of extension study drug + 30 days will also be excluded from analysis.

Table 10: Visit Windows for Mammogram Assessments

Visit	Start Day	Target Day	End Day
Week 52	309	365	421
Week 104	675	731	787

For patients who are or become ≥ 40 years old during the study.

Mammogram assessments are required only by protocol amendment 3.0 and 3.1.

Table 11: Time Windows for Daily Assessments from eDiary

Visit	Target Study Day of Visit[a]	Days Included in Assessment Period Window
Week 4	X_1	1 to X_1
Week 8	X_2	$(X_2 - 34)$ to $\leq X_2$
Week 12	X_3	$(X_3 - 34)$ to $\leq X_3$
Week 16	X_4	$(X_4 - 34)$ to $\leq X_4$
Week 20	X_5	$(X_5 - 34)$ to $\leq X_5$
Week 24	X_6 [b]	$(X_6 - 34)$ to $\leq X_6$
Week 28	X_7	Maximum [OLE start day [c], $(X_7 - 34)$] to $\leq X_7$
Week 32	X_8	Maximum [OLE start day [c], $(X_8 - 34)$] to $\leq X_8$
Week 36	X_9	$(X_9 - 34)$ to $\leq X_9$
Week 40	X_{10}	$(X_{10} - 34)$ to $\leq X_{10}$
Week 44	X_{11}	$(X_{11} - 34)$ to $\leq X_{11}$
Week 48	X_{12}	$(X_{12} - 34)$ to $\leq X_{12}$
Week 52	X_{13}	$(X_{13} - 34)$ to $\leq X_{13}$
Week 65[g]	X_{14}	$(X_{14} - 56)$ to $\leq X_{14}$
Week 78[g]	X_{15}	$(X_{15} - 56)$ to $\leq X_{15}$
Week 91[g]	X_{16}	$(X_{16} - 48)$ to $\leq X_{16}$
Week 104[g]	X_{17}	$(X_{17} - 51)$ to $\leq X_{17}$
Week104/EOT[e]	X_{17}	Maximum [OLE start day [c], $(X_{17} - 34)$] to $\leq X_{17}$ or PAP [f]

Abbreviation: EOT = end of treatment, OLE = open label extension.

Error! Reference source not found. Refer to **Error! Reference source not found.**Table 3 for target study day for Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 65, 78, 91, 104 and safety Follow-Up.

[b] The target study day for Week 24 is defined as date of last dose of randomized study treatment in pivotal phase 3 study. The Week 24 assessment period is defined as the 35 days up to and including the date of last dose of randomized study treatment in pivotal phase 3 study, which should occur on the day prior to the Week 24 visit.

[c] OLE start day = day of first dose administered of extension study treatment.

[e] The target study day for Week 104/EOT for purposes of visit window calculations is defined as date of last dose of study treatment in the extension study.

[f] If the last 35 calendar days prior to and including date of last dose of study drug are not entirely within an eDiary collection period, then days of the pain assessment period (PAP) will be determined as follows: (1) if the date of last dose occurs during the eDiary collection period, the PAP will be the last 35 days which are counted during up to two eDiary collection periods immediately prior to and including date of last dose of study drug (2) if the date of last dose occurs outside of the eDiary collection period, the PAP will be the last 35 days which are counted during up to two eDiary collection period(s) immediately prior to but not including date of last dose of study drug.

[g]: For Week 65, Week 78, Week 91 and Week 104, only data collected within eDiary cycles required by protocol is included in the analysis.

4.4. General Rules for Missing Data

The rules for handling missing data for by-visit endpoints and incomplete dates associated with adverse events and concomitant medications are discussed in this section. Handling of missing data for the primary efficacy analyses are described in Section 7.2.4.

4.4.1. 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.

4.4.2. 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 extension study treatment start date, then set to extension study treatment start date, as long as adverse event end date is not prior to extension study treatment start date;
  - If both Month and Day are missing and Year ≠ Year of extension study treatment start date, then set to January 1;
  - If Day is missing and Month and Year = Month and Year of extension study treatment start date, then set to extension study treatment start date, as long as adverse event end date is not prior to extension study treatment start date;
  - If Day is missing and Month and Year ≠ Month and Year of extension study treatment start date, then set to first of the month;
  - If start date is completely missing, set to extension study treatment start date, as long as adverse event end date is not prior to pivotal phase 3 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.

4.5. Handling Multiple Values on the Same Day

Questionnaires

If a questionnaire (eg, PGA, PGIC, or EHP-30) is completed multiple times on the same day, then the questionnaire assessment with the worst score will be used for analysis.

eDiary Entries

If there are multiple eDiary entries (NRS, sB&B) on the same day for a patient, then the worst score (eg, higher pain score) will be used for analysis.

If there are multiple eDiary entries (analgesics) reported on the same day but at different time for a patient, then all pills reported at different time will be used for analysis. If there are multiple eDiary entries (analgesics) on the same day and at the same time, then the record with the last modified time will be used for that time.

5. STUDY POPULATION

5.1. Subject Disposition

The number and percentage of patients for each of the following categories will be summarized by pivotal phase 3 study treatment group in final analysis:

- All patients enrolled defined as taking the first dose of study drug in the Extension Study;
- Patients included in the Extension Study population;
- Patients included in the Extension Safety population.

In final analysis, the number and percentage of patients for each of the following categories will be summarized by pivotal phase 3 study treatment group:

- Patients who completed 52 weeks treatment (24 weeks pivotal study treatment period and 28 weeks open-label treatment period)
- Patients who completed the 104 weeks of treatment (24 weeks pivotal study treatment period and 80 weeks open-label treatment period);

- Patients who discontinued early from the 80 weeks open-label treatment period and reasons for discontinuation;
- Patients who entered the BMD post-treatment Follow-Up period.

5.2. Protocol Deviations

Protocol deviations that occurred during the extension study will be categorized as important or minor per the most updated version of 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 Study 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 pivotal phase 3 study treatment group in Extension Study Population. Categorical data will be summarized using frequencies and percentages, by pivotal phase 3 study treatment group and overall (see Table 12le 12). Summaries of continuous data will display the mean, SD, median, minimum, and maximum. The numbers of missing values will also be summarized.

Table 12: Categories for Demographic and Baseline Characteristics

Variable	Category
Age (years)	< 35, ≥ 35
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)	< 18.5, 18.5 to <25, 25 to <30, 30 to < 35, 35 to < 40, ≥ 40
Time Since Surgical Diagnosis of Endometriosis (years)	< 5, ≥ 5 < 2, 2 to < 5, ≥ 5
Alcohol Consumption History	None, Moderate, Heavy

Smoking History	Never smoker, Former smoker, Current smoker
Analgesic Use (During Run-In Period in pivotal phase 3 study)	None, Tier 1 only, Tier 2 only, Both Tier 1 and Tier 2
Dysmenorrhea NRS Score	< 7, ≥ 7 < 4, 4 to < 7, 7 to 10
NMPP NRS Score	< 4, ≥ 4 < 4, 4 to < 7, 7 to 10
EHP-30 Pain Domain Score	0 to < 25, 25 to < 50, 50 to < 75, 75 to 100
Patient Global Assessments	
Dysmenorrhea	Absent, Mild, Moderate, Severe, Very Severe
NMPP	Absent, Mild, Moderate, Severe, Very Severe
Function	Not at all, Minimally, Moderately, significantly, very significantly
Overall Pelvic Pain	Absent, Mild, Moderate, Severe, Very Severe
American Fertility Society of Endometriosis Stage	I Minimal; II Mild; III Moderate; IV Severe; Unknown/Not Available
Bone Mineral Density	
Lumbar L1-L4	Mean (SD), median, min, max
Total Hip	Mean (SD), median, min, max
Femoral Neck	Mean (SD), median, min, max
Renal Function [a]	CrCl: < 60, ≥ 60 to < 90, ≥ 90 mL/min

Abbreviations: BMI = body mass index; CrCl = creatinine clearance; EHP-30 = Endometriosis Health Profile 30-Item Questionnaire; NMPP = non-menstrual pelvic pain; NRS = numerical rating scale; SD = standard deviation.
[a] Creatinine clearance by Cockcroft-Gault Equation = 0.85 × {(140 – age(years)) × weight(kg)}/(72 × Serum Creatinine(mg/dL)) for women.

5.4. Medical History

Medical history collected at the time of entry into the pivotal phase 3 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 Study Population. Additionally, summaries of endometriosis–specific medical history, and historic medical and surgical treatments collected at the time of entry into the pivotal phase 3 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. Concomitant Medications

Concomitant medications taken during the extension study treatment period and overall treatment period will be summarized for all patients in the Extension Safety Population by pivotal phase 3 study treatment group. Medications are considered concomitant during the extension study if exposure starts prior to the pivotal phase 3 study and continues in the extension treatment period, or exposure starts during the pivotal phase 3 study and continues in

the extension treatment period, or exposure starts during the extension study and continues in the extension treatment period. Medications are considered as overall concomitant if exposure starts prior to the pivotal phase 3 study, starts during the pivotal phase 3 study, or starts during the extension study, with exposure ending in the pivotal phase 3 study period, ending in the extension treatment period, or continuing after the extension treatment period.

A patient who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

Certain medication types will be summarized separately, including Tier 1 analgesics, Tier 2 analgesics, all analgesics, hormonal contraceptives, estrogens, progestins, other hypothalamic-pituitary-gonadal axis affecting drugs, calcium supplements, vitamin D supplements, and glucocorticoids.

6. STUDY DRUG EXPOSURE AND COMPLIANCE

All analyses of study drug exposure and compliance will be summarized by actual treatment received in the pivotal phase 3 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 pivotal phase 3 study and extension study will be summarized by pivotal Phase 3study treatment group. Compliance with open-label study drug during the extension study for the Extension Safety population will be summarized by pivotal phase 3 study treatment group. Overall compliance with study drug throughout the pivotal phase 3 study and extension study will be summarized by pivotal phase 3 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 pivotal phase 3 and extension studies, will be summarized by pivotal phase 3 study treatment group. Treatment duration during the extension study and overall with any study drug (relugolix, E2/NETA, or placebo) will be summarized by pivotal phase 3 study treatment group.

Study drug compliance will be summarized for the extension study treatment period and for the overall pivotal phase 3 and extension study treatment period, and will be calculated as follows:

$$(\text{total tablets taken} / \text{total tablets expected to be taken}) \times 100$$

The total tablets taken will be calculated as:

$$(\text{total tablets dispensed} - \text{total tablets returned})$$

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 extension study treatment period, or throughout the pivotal phase 3 and extension study treatment period. Tablets that were dispensed and not returned will be assumed to have been taken. For patients without dose interruption, expected number of tablets is calculated as (last dose date of any of

the study drug – first dose date of study drug) + 1. In the final analysis, 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 by pivotal phase 3 study treatment group. No formal treatment comparisons will be performed for this extension study. As there are no inferential statistics for these analyses, there is no need for multiplicity adjustment.

The pivotal phase 3 study Baseline will be used as the reference point for this extension study for the analyses of change from baseline. The pain scores during the Baseline Pain Assessment Period of the pivotal phase 3 study will establish the patient's baseline for both the pivotal phase 3 study and the extension study.

For the final analyses, efficacy outputs will include all data up to Week 104. Study visits include each monthly visit from Week 4 to Week 52 and each quarterly visit after Week 52.

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 pivotal phase 3 study treatment group and by 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 pivotal phase 3 study 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 pivotal phase 3 study treatment group.

For endpoints evaluating the change (absolute or percent change) from Baseline to Week 52 or Week 104/EOT, mean change as well as least squares (LS) means change and 95% CI will be summarized. LS means and 95% CI will be derived using a mixed-effects model repeated

measures approach with pivotal Phase 3study randomization stratification factors, visit, treatment, and treatment-by-visit interaction included as fixed effects. Here treatment refers to pivotal Phase 3study treatment group. The Baseline value will be included as a covariate, and an unstructured variance-covariance matrix will be assumed. If the mixed-effects 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 Endpoints

The primary endpoints will be referred to as responder rates and derived on the basis of reduction of pain score and no increase in use of analgesic medications as recorded in a daily eDiary (see Section 7.2.5 for details).

The primary efficacy endpoints of the study for the final analyses are for Week 52 and Week 104/EOT.

The primary efficacy endpoints of the study for the Week 52 analyses are:

- Proportion of patients who meet the DYS responder criteria at the Week 52 pain assessment period, achieving a mean reduction in DYS NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary;
- Proportion of patients who meet the NMPP responder criteria at the Week 52 pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily eDiary;

The primary efficacy endpoints of the study for Week 104/EOT are:

- Proportion of patients who meet the DYS responder criteria at the Week 104/EOT pain assessment period, achieving a mean reduction in DYS NRS scores of at least 2.8 points and no increase in use of analgesic medications as recorded in a daily eDiary;

  Proportion of patients who meet the NMPP responder criteria at the Week 104/EOT pain assessment period, achieving a mean reduction in NMPP NRS scores of at least 2.1 points and no increase in use of analgesic medications as recorded in a daily.

7.2.1. Primary Efficacy Analysis

The responder rate and two-sided 95% CI will be presented by the pivotal phase 3 study treatment group. No treatment comparisons will be performed for this extension study. For the primary analyses, both primary endpoints will incorporate the missing data handling rules described in Section 7.2.6.

7.2.2. Determination of the Meaningful Change Thresholds for the Primary Endpoints

The responder threshold of DYS and NMPP used in pivotal phase 3 studies will be applied to this extension study. For DYS, the responder threshold was determined as a 2.8-point improvement. For NMPP, the responder threshold was determined as a 2.1-point improvement. The derivation of the prespecified meaningful change thresholds (MCTs) for the primary

endpoints was done by anchor-based analyses (see Appendix 3 of the pivotal phase 3 study statistical analysis plan version 1.2).

7.2.3. Data Sources Supporting Derivation of Responder Status

The data sources used to determine the responder status for the dysmenorrhea and NMPP responder efficacy endpoints are listed below:

- Patient report of NRS pain scores (dysmenorrhea and NMPP), menstruation status, and use of protocol specified analgesics for pelvic pain as captured in the eDiary;
- Menstruation status as recorded on the CRF page at each visit.

Further details of the derivation of the responder status for the primary efficacy endpoints are described in the pivotal phase 3 study SAP version 1.2 Section 7.2.5.

7.2.4. Definitions Related to Numerical Rating Scale Pain Scores and Analgesic Use

Dysmenorrhea NRS Scores

Dysmenorrhea NRS pain scores are pain scores reported in the eDiary on days that the patient reports she is bleeding. Non-menstrual pelvic pain NRS pain scores are those pain scores reported in the eDiary on days that the patient reports she is not bleeding.

Baseline Assessment of NRS Pain Scores and Analgesic Use

Pivotal phase 3 study baseline NRS pain scores will be used as baseline NRS pain scores in the extension study analyses. Baseline NRS pain scores for DYS and NMPP are the averages of the respective eDiary pain scores reported during the baseline pain assessment period.

Pivotal phase 3 study baseline analgesic use for pelvic pain will be used as baseline analgesic use in the extension study analyses. It is the average daily pill count as reported in the eDiary during the pivotal phase 3 study baseline pain assessment period. The baseline average daily pill count will be calculated separately for Tier 1 and Tier 2 analgesics.

Week 52 and Week 104/EOT Assessment of NRS Pain Scores and Analgesic Use

The Week 52 pain scores for DYS and NMPP are the averages of the respective eDiary pain scores reported during the Week 52 pain assessment period (PAP), defined as the last 35 calendar days of extension study treatment immediately prior to Week 52. For patients with extension study treatment duration less than 35 days, Week 52 PAP is defined as the days between the first dose of extension study drug and date of last dose of extension study drug.

Week 52 analgesic use for pelvic pain is the average daily pill count as reported in the eDiary during the Week 52/ PAP. The average daily pill count will be calculated separately for Tier 1 and Tier 2 analgesics for Week 52.

Since eDiary is not required to report out of the eDiary collection cycle, ie. Week 53 - 57, Week 66 - 70, Week 79 - 84 and Week 92 - 97, study days in those periods would not be included in the Week 104/EOT pain assessment period or analgesic use for primary endpoints analyses.

The Week 104/EOT pain scores for DYS and NMPP are the averages of the respective eDiary pain scores reported during the Week 104/EOT PAP, defined as

- If the last 35 calendar days prior to and including date of last dose of extension study drug are entirely within an eDiary collection period, then the PAP will be the last

35 calendar days immediately prior to and including the date of last dose of study drug;

- If the date of last dose occurs outside of the eDiary collection period or there are not 35 calendar days prior to the last dose of extension study drug from the eDiary collection period that includes the last dose, the PAP will be the last 35 days in the eDiary collection day on or prior to the last dose of study drug, from the last one or two eDiary collection periods.
- If the last 35 calendar days prior to and including date of last dose of study drug are not entirely within an eDiary collection period:
  - if the date of last dose occurs during the eDiary collection period, the PAP will be the last 35 days which are counted during up to two eDiary collection periods immediately prior to and including date of last dose of study drug
  - if the date of last dose occurs outside of the eDiary collection period, the PAP will be the last 35 days which are counted during up to two eDiary collection period(s) immediately prior to but not including date of last dose of study drug

Week 104/EOT analgesic use for pelvic pain is the average daily pill count as reported in the eDiary during the Week 104/EOT PAP. The average daily pill count will be calculated separately for Tier 1 and Tier 2 analgesics for Week 104/EOT.

NRS pain scores and analgesic use during PAP of each of other study weeks will be calculated for efficacy analysis by visit. Pain scores for DYS and NMPP are the averages of the respective eDiary pain scores reported during each individual PAP. Analgesic use for pelvic pain is the average daily pill count as reported in the eDiary during each individual PAP.

For Week 65, 78, 91 and 104, PAP is defined as the total days of ediary collection period immediately prior to respective week. For Week 28 to Week 48, PAP is defined as the last 35 calendar days of extension study treatment immediately prior to respective week. For patients with extension study treatment duration less than 35 days, PAP is defined as the days between the first dose of extension study drug and date of last dose of extension study drug.**Definition of Increased Use of Analgesics**

The definition of increased analgesic use in pivotal phase 3 studies will be applied to this extension study. Protocol-specified analgesic medications for endometriosis-associated pain will be analyzed based on the following categories:

- Tier 1
  - Ibuprofen (200 mg)
- Tier 2:
  - Tramadol (37.5 mg)/Paracetamol (325 mg)
  - Tramadol (50 mg)
  - Codeine (30 mg)
  - Codeine (30 mg)/Paracetamol (300 mg)
  - Codeine (30 mg)/Paracetamol (500 mg)

- Codeine (15 mg)/Paracetamol (500 mg)
- Hydrocodone (5 mg)/Paracetamol (325 mg)

The Tier 2 analgesics prescribed for use in the study was country specific. Patients will record their use of these medications in an eDiary every day until Week 52 and after Week 52, eDiary scores will be entered over four eDiary collection cycles on following schedules: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit. This will include the information on medication name, dosage, usage of medication (eg, for endometriosis-associated pelvic pain or not), and total number of pills taken. The percent change in analgesic use between the pivotal phase 3 study baseline and Week 52will be calculated as absolute change in analgesic use from pivotal phase 3 study baseline to Week 52 divided by pivotal phase 3 study baseline analgesic use. The percent change in analgesic use between the pivotal phase 3 study baseline and Week 104/EOT will be calculated as absolute change in analgesic use from pivotal phase 3 study baseline to Week 104/EOT divided by pivotal phase 3 study baseline analgesic use. For the primary endpoints of DYS and NMPP, patients will be considered as non-responders if they have an increase in rescue analgesic use as specified in Table 13.

Table 13: Effect of Protocol-Specific Analgesic Medication Use for Endometriosis-Associated Pain on Responder Status at Week 52, Week 104/EOT

Analgesic Use for EAP at Pivotal phase 3 study Baseline	Tier 1 Analgesic Use for EAP		Tier 2 Analgesic Use for EAP	Analgesic Responder Status[a]
Missing all eDiary data during extension study				
n/a	n/a		n/a	Baseline/Week 24 analgesic responder status from pivotal phase 3 study
At least one eDairy data during extension study				
No analgesic use	Any use	**OR**	Any use	Non-responder
	No use	**AND**	No use	Responder
Used Tier 1 analgesic only	Use increased > 15% from baseline	**AND**	No use or any use	Non-responder
	Any use or no use	**AND**	Any use	
	Use stopped, decreased, or stable	**AND**	No use	Responder
Used Tier 2 analgesic only	Any use or no use	**AND**	Use increased > 15% from baseline	Non-responder
	Any use	**AND**	Use is stable	
	No use	**AND**	Use stopped, decreased, or stable	Responder
	Started use	**AND**	Use stopped or decreased	

Analgesic Use for EAP at Pivotal phase 3 study Baseline	Tier 1 Analgesic Use for EAP		Tier 2 Analgesic Use for EAP	Analgesic Responder Status[a]
Used Tier 1 and Tier 2 analgesics	Use increased > 15% from baseline	**AND**	Use stable or increased > 15% from baseline	Non-responder
	Stable use	**AND**	Use increased > 15% from baseline	
	Use decreased	**AND**	Use increased > 15% from baseline	
	Use stopped	**AND**	Use increased > 15% from baseline	
Used Tier 1 and Tier 2 analgesics	Use increased > 15% from baseline	**AND**	Use stopped or decreased	Responder
	Stable use	**AND**	Use stopped, decreased, or stable	
	Use decreased	**AND**	Use stopped, decreased, or stable	
	Use stopped	**AND**	Use stopped, decreased, or stable	

Abbreviations: EAP = endometriosis-associated pain; EOT = end of treatment.

[a] Non-responder = patient will be considered a non-responder for each of the primary endpoints; Responder = patient may be classified as a responder for the dysmenorrhea or non-menstrual pelvic pain primary endpoints if there is also a sufficient reduction in dysmenorrhea or non-menstrual pelvic pain (as determined by the appropriate responder threshold), respectively, from baseline to Week 52, or to Week 104/EOT.

7.2.5. Definition of Responder at Week 52 and Week 104/EOT

A DYS responder is defined separately for Week 52 and Week 104/EOT. A DYS responder is defined as a patient with data that satisfies each of the following:

- had a reduction in average DYS NRS pain score from pivotal phase 3 study baseline of at least 2.8 points, or had a DYS NRS pain score ≤ 0.1 at Week 52 or Week 104/EOT if the pivotal phase 3 study baseline DYS pain score was less than 2.8;
- did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with pivotal phase 3 study baseline use (Table 14) at Week 52 or Week 104/EOT.

An NMPP responder is defined separately for Week 52 and Week 104/EOT. An NMPP responder is defined as a patient with data that satisfies each of the following:

- had a reduction in average NMPP NRS pain score from baseline of at least 2.1 points, or had a NMPP NRS pain score ≤ 0.1 at Week 52 or Week 104/EOT if the pivotal phase 3 study baseline NMPP pain score was less than 2.1;
- did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with pivotal phase 3 study baseline use (Table 15) at Week 52 or Week 104/EOT.

The reduction from baseline in DYS or NMPP pain scores at Week 52, or Week 104/EOT will be calculated separately as the absolute difference between the respective average pain score at Week 52, or Week 104/EOT and the average pain score at pivotal phase 3 study baseline. According to the description given above, patients who have an average baseline DYS or NMPP score smaller than the corresponding meaningful change threshold may still be classified as a responder if their average pain score at Week 52, or Week 104/EOT is no more than 0.1. This condition is strict and can only be met when nearly all daily pain scores from the assessment period are 0, with the very few remaining daily pain score(s) being minimal.

The responder status for DYS or NMPP at Week 52, Week 104/EOT will be assessed based on the reduction from pivotal phase 3 study baseline in average pain scores (ie, whether there is a reduction of at least the meaningful change threshold as described above), change from pivotal phase 3 study baseline in use of rescue analgesic medications, compliance with eDiary entry over the Week 52, Week 104/EOT pain assessment period, and menstruation status per the eCRF. Further details of the derivation of responder status are given in Section 7.2.6.

7.2.6. Derivation of Responder Status at Week 52, Week 104/EOT and Missing Data Handling Rules

For the primary efficacy analysis, both primary endpoints will incorporate the missing data handling rules at Week 52, Week 104/EOT as follows (Table 14, Table 15 and Figure 2):

- For patients missing eDiary for all visits in the extension study, their Baseline/Week 24 responder status from the pivotal phase 3 study will be carried over as their responder status to Week 52, Week 104/EOT.
- For patients who have any pain score entries in eDiary in the extension study, responder status for DYS and NMPP will be derived as follows:
  - For DYS, the responder status will be defined using the following rules taking analgesic use into consideration (Table 14):
    - If there are at least 2 days of DYS NRS scores reported in the eDiary, then the average will be calculated and used in the assessment of the DYS responder status. Requiring a minimum of 2 days of DYS NRS scores is considered reasonable since a typical menstrual cycle has bleeding days ranging from 3 to 7 days.
    - If there are < 2 days of NRS scores for DYS reported in the eDiary, then the following scenarios will be considered:
      - If no DYS scores are reported in the eDiary, then the data collected on the menstruation eCRF will be considered as follows:
        - If no menstruation is reported on the eCRF, then the average DYS score will be set as 0;
        - Otherwise, if any menstruation days are reported on the eCRF, then the average DYS score will be set as missing and will be imputed using a mixed-effects model.

- If only one DYS score is reported in the eDiary, then the data collected on the menstruation eCRF will be considered as follows:
  - If no more than one menstruation day is reported on the eCRF, then the observed DYS score will be taken as the average DYS score;
  - If more than one menstruation day is reported on the eCRF, then the average DYS score will be considered missing and will be imputed using a mixed-effects model.

– For NMPP, the responder status will be defined using the following rules, taking analgesic use into consideration (Table 15):
  - If there are at least 14 days of scores for NMPP reported in the eDiary, then the average NMPP score will be used in the assessment of the NMPP responder status. Requiring minimum 14 days of NMPP scores is considered reasonable since this corresponds to at least half of the non-menstrual days from a typical 28-day menstrual cycle.
  - If there are less than 14 days of NMPP scores in the eDiary, then the average NMPP score will be considered missing and will be imputed using predicted values from a mixed-effects model.

Table 14: Missing Data Handling Rules for Average Dysmenorrhea NRS Score at Week 52, Week 104/ EOT

Number of Days with DYS Scores Reported in eDiary	Menstruation Status per eCRF	Average DYS Score Status	Responder Status[a]
Missing all eDiary data during extension study			
n/a	n/a	n/a	Baseline/Week 24 responder status from pivotal phase 3 study
Having at least one eDiary data during extension study			
≥ 2 days	n/a	Observed	Based on observed change from baseline and analgesic use
1 day	No more than 1 menstruation day reported	Observed	Based on observed change from baseline and analgesic use
	More than 1 menstruation day reported	Missing (to be imputed from mixed-effects model)	Based on imputed change from baseline and analgesic use
0 days	No menstruation days reported	Assigned as 0	Based on change from baseline and analgesic use
	At least 1 menstruation day reported	Missing (to be imputed from mixed-effects model)	Based on imputed change from baseline and analgesic use

Abbreviations: eCRF = electronic case report form; eDiary = electronic diary; n/a = not applicable.

[a] Determined by comparing the observed (or imputed) change from baseline to the responder threshold and by examination of change from baseline in analgesic use.

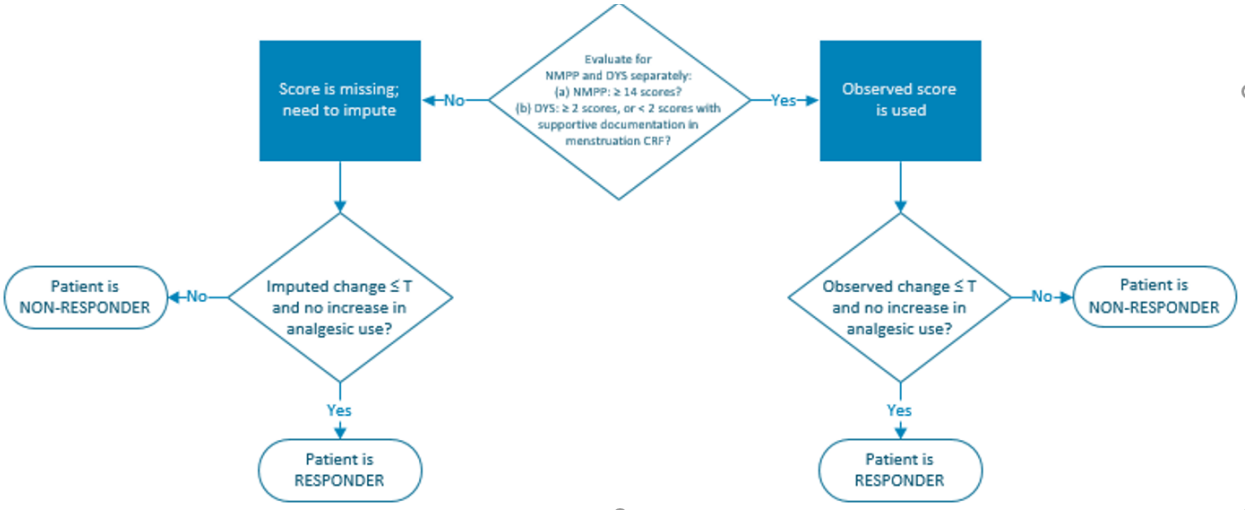
Table 15: Missing Data Handling Rules for Average Non-Menstrual Pelvic Pain NRS Score at Week 52, Week 104/EOT

Number of Days with NMPP Scores Reported in eDiary	Average NMPP Score Status	Responder Status[a]
Missing all eDiary data during extension study		
n/a	n/a	Baseline/Week 24 responder status from pivotal phase 3 study
At least one eDiary data during extension study		
≥ 14 days	Observed	Based on observed change from baseline and analgesic use
< 14 days	Missing (to be imputed from mixed-effects model)	Based on imputed change from baseline and analgesic use

Abbreviations: eDiary = electronic diary; n/a = not applicable; NMPP = non-menstrual pelvic pain.

[a] Determined by comparing the observed (or imputed) change from baseline to the responder threshold and by examination of change from baseline in analgesic use.

Figure 2: Visual Depiction of the Missing Data Handling Rules and Determination of Responder Status for the Primary Efficacy Endpoints



Abbreviations: CRF = case report form; DYS = dysmenorrhea; EOT = end of treatment; NMPP = non-menstrual pelvic pain.

T represents the responder threshold (-2.8 for dysmenorrhea and -2.1 for NMPP) determined from the anchor-based analyses.

7.2.7. Mixed-Effects Model for Imputing Missing or Partially Missing Pain Scores at Week 52 and Week 104/EOT

For the primary analysis in the final analysis, patients with missing pain scores at Week 52, Week 104/EOT will be identified separately for DYS and NMPP, per the missing data handling rules described above. For imputing missing data for the primary analysis of each primary endpoint, a mixed-effects model approach will be used to derive predicted average pain scores,

as the mixed-effects approach may better describe the effects of a hormonal treatment (such as suppression of the hypothalamic-pituitary-ovarian axis by gonadotropin-releasing hormone (GnRH) receptor antagonists) than other imputation methods, such as multiple imputation.

Specifically, a mixed-effects model with repeated measures of average pain scores at multiple time points will be fitted to predict change in average pain scores from baseline (as a dependent variable) through the fixed-effects associated with covariates (ie, stratification factors of years since endometriosis diagnosis at pivotal phase 3 study baseline and geographic region, visit, treatment, treatment-by-visit interaction, pivotal phase 3 study baseline average NRS score,) and random effects (from the individual patients). Here treatment refers to pivotal Phase 3 pivotal phase 3 study treatment group. In this model, an unstructured variance-covariance matrix is assumed for each patient. If the mixed-effects model fails to converge, a first-order autoregressive variance-covariance matrix will be used. Multiple time points at Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 65, 78, 91, 104 and 104/EOT will be used for the analyses.

Sample SAS code is provided below for illustration. The specification of type=UN implements unstructured variance-covariance matrix for an individual patient with multiple measures of average pain scores. If the model fails to converge, then variance-covariance matrix structure will be specified as first-order autoregressive (ie, AR(1)).

```
proc mixed data=NRS_dataset method=REML covtest;
class PID DXYRS REGION VISIT TRT;
model CHG_NRS = DXYRS REGION BASE VISIT TRT VISIT*TRT/ s  outp=emmi_mixed_p covb
outp=emmi_mixed_p covb;
repeated VISIT / type=UN subject=PID r;
lsmeans  VISIT*TRT;
ods output SolutionF=mixparms CovB=mixcovb;
```

BASE is the pivotal phase 3 study baseline pain score; CHG_NRS is change in average pain score from pivotal phase 3 study baseline to Week 104/EOT as the dependent variable; DXYRS is a randomization stratification factor (years since endometriosis diagnosis: < 5 versus ≥ 5); PID is patient identification number; REGION is a randomization stratification factor (North America versus rest of world); TRT is pivotal phase 3 study treatment group (relugolix + E2/NETA, relugolix + delayed E2/NETA, placebo); VISIT is visit time point.

Applying this model over the observed longitudinal average NRS score data, the fixed-effects will be estimated and the relationship of change in average NRS scores from pivotal phase 3 study baseline with the covariates will be characterized by the fitted model. From the fitted model, the change in average NRS scores (whether missing or not) will be predicted for each patient at each visit and in a particular stratum. The imputed average NRS scores at Week 52 or Week 104/EOT will be obtained by adding the pivotal phase 3 study baseline average NRS scores to the difference.

Since the purpose of using the mixed-effects model is to impute the missing average NRS scores identified at Week 52 or Week 104/EOT as described above, the predicted average NRS scores from the model at the corresponding Week 52 or Week 104/EOT visit (at which the missing average NRS scores are identified) will be used in the determination of responder status. For patients without the need for imputation, their responder status will be derived based on the observed data according to the algorithms laid out in Figure 2.

This imputation approach is consistent with the definition of responder at Week 52, Week 104/EOT for the primary endpoints.

7.2.8. Subgroup Analyses

Subgroup analyses of the dysmenorrhea and NMPP responder analyses at Week 104/EOT will be performed to assess whether responder rate is consistent across clinically important subgroups. The responder rate and 95% CI may be displayed for each subgroup. 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 (years)	< 35, >= 35; < 30, 30 to < 35, 35 to < 40, ≥ 40
Race	Black or African American, White
BMI (kg/m^2) at Baseline	< 30, ≥ 30; < 18.5, 18.5 to < 25, 25 to < 30, 30 to < 35, 35 to < 40, ≥ 40; <25, 25 to < 30, >=30

Abbreviations: BMI = body mass index;

7.3. Secondary Efficacy Endpoints

All secondary efficacy measures over the course of both the pivotal phase 3 and extension studies will be presented by the pivotal phase 3 study treatment group using descriptive statistics. No treatment comparisons will be performed for this extension study.

7.3.1. Change from Baseline in EHP-30 Pain Domain Scores

No imputations will be made for missing values in the EHP-30 Pain Domain scores.

The score for an EHP-30 domain is calculated by adding the scores for individual items (each with five response options scored from 0 to 4) to obtain a total raw score, then dividing by the highest possible raw score and multiplying the result by 100 to obtain a normalized score that ranges from 0 to 100. For each domain, the normalized score is:

$$\text{Normalized score} = (\text{Total raw score} / \text{Total raw score range}) \times 100$$

The normalized score is used for analysis. Higher scores represent a greater (ie, more negative) functional impact of endometriosis. The domains are provided in Table 17.

The mean change and percent change from pivotal phase 3 study baseline by visit of pivotal phase 3 study and extension study will be analyzed for pain domain and each of the non-pain domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image). LS means and 95% CI are based on mixed-effects model with visit, treatment, treatment-by-visit interaction, region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, >=5 years), and baseline value included as fixed effects. The multiple visits for each patient are the repeated measures as random effects within each patient, and an unstructured covariance matrix is assumed. If the mixed-effects model fails to converge, a first-

order autoregressive variance-covariance matrix will be used. Here treatment refers to pivotal phase 3 study treatment group.

In addition, proportion of patients who are responders of EHP-30 pain domain will be determined and summarized by pivotal phase 3 study treatment group. The prespecified clinically meaningful threshold of ≥ 20 points decrease from baseline will be used.

Responder rate and two-sided 95% CI based on Clopper-Pearson exact binomial will be presented for Week 52 and Week 104. For each question of the EHP-30 Pain Domain, the proportion of patients in each category at Week 52 and Week 104 will be described. The percentage of patients shifting from Baseline "often/always" to post-baseline "never/rarely" will also be summarized for each question at Week 52 and Week 104.

Table 17: Endometriosis Health Profile 30-Item Questionnaires Scores

Domain	Items	Lowest and Highest Possible Total Raw Scores	Total Raw Score Range
Pain	1 – 11	0, 44	44
Control and Powerlessness	12 – 17	0, 24	24
Emotional Well-Being	18 – 23	0, 24	24
Social Support	24 – 27	0, 16	16
Self-Image	28 – 30	0, 12	12

7.3.2. Change from Baseline in Numerical Rating Scale Score for Endometriosis-Associated Pain

Patients assessed endometriosis-associated pain using an NRS as part of their daily eDiary entries. Patients rated their worst pelvic pain in the past 24 hours on a scale from 0 to 10, with 0 indicating no pain and 10 indicating pain as bad as you can imagine. Patients also recorded whether they had menstruated in the past 24 hours. The mean NRS score for DYS during the Week 52, Week 104/EOT pain assessment period is calculated as the average of the pain scores recorded on days for which patients reported they were menstruating. The mean NRS score for NMPP during the Week 52, Week104/EOT pain assessment period is calculated as the average of the pain scores recorded on days on which patients reported they were not menstruating. The mean NRS scores for DYS and NMPP are calculated in a similar manner during the pivotal phase 3 studies baseline pain assessment period.

The mean NRS score of overall pelvic pain for Week 52 and Week 104/EOT pain assessment periods will be based on all pain scores recorded without regard for menstruation status. The mean NRS score of dyspareunia for Week 52 and Week 104/EOT pain assessment periods will be based on the pain scores recorded on days when the patient reported having vaginal sexual intercourse. This analysis will be performed in the subgroup of patients with baseline dyspareunia defined as having a non-zero baseline dyspareunia score.

The mean change and percent change of NRS score from baseline to Week 52, and to Week 104/EOT will be presented by the pivotal phase 3 study treatment group for DYS, NMPP, overall pelvic pain, and dyspareunia separately. LS means and 95% CI are based on mixed-effects model with visit, treatment, treatment-by-visit interaction, region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, >=5 years), and baseline

value as fixed effects; The multiple visits for each patient are the repeated measures as random effects within each patient, and an unstructured covariance matrix is assumed. Here treatment refers to pivotal phase 3 study treatment group.

The number and percentage of patients with following NRS categories will be presented by visit and by the pivotal phase 3 study treatment group for DYS, NMPP separately.

- < 4 vs >= 4
- < 4, 4 - < 7, 7 – 10

7.3.3. Analgesic use

Protocol-specified analgesics (see section 7.2.4) for endometriosis-related pain will be analyzed. Proportion of patients not using protocol-specified opioids for endometriosis-associated pain at Week 52, and Week 104/EOT will be presented by pivotal phase 3 study treatment group and by visit. Proportion of patients not using protocol-specified analgesics for endometriosis-associated pain at Week 52, and Week 104/EOT will be presented by pivotal phase 3 study treatment group and by visit. Two-sided 95% CIs for the proportions will be generated based on Clopper-Pearson exact binomial.

7.3.4. Change from Baseline in Patient Global Assessments

The PGAs for overall pelvic pain and function impairment use a 5-point response scale. To calculate change from pivotal phase 3 studies baseline to Week 52, and Week 104, the numerical scores shown in Table 18 Table 1will be assigned to each response level.

Table 18: Patient Global Assessment Numerical Scores

Function	Overall Pelvic Pain	Numerical Score
Not at all	Absent	0
Minimally	Mild	1
Moderately	Moderate	2
Significantly	Severe	3
Very Significantly	Very Severe	4

The number and percentage of patients in each severity of PGA category will be presented by pivotal phase 3 study treatment group. The mean change of total PGA score from pivotal phase 3 study Baseline will be presented for overall pelvic pain and function separately by visit and by pivotal phase 3 study treatment group. LS means and 95% CI are based on mixed-effects model with visit, pivotal phase 3 study treatment group, treatment-by-visit interaction, region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, >=5 years), and baseline value included as fixed effects; The multiple visits for each patient are the repeated measures as random effects within each patient, and an unstructured covariance matrix is assumed. Here treatment refers to pivotal phase 3 study treatment group. Least squares mean and 95% CI will be presented by pivotal phase 3 study treatment group and by visit. The categorical changes of amount of improvement of PGA for overall pelvic pain from baseline to Week 52, and to Week 104 will be summarized by pivotal phase 3 study treatment group and by

visit. Proportion of patients with PGA for function Improvement, No Change, and Worsening from Baseline will be presented by pivotal phase 3 study treatment group and by visit.

7.3.5. Change from Baseline in Functional Impairment on sB&B Scale

The daily eDiary completed by patients includes assessments of endometriosis-associated pain by the sB&B scales for DYS, pelvic pain, and dyspareunia. The dysmenorrhea and dyspareunia scales have possible scores of 0 to 4, while the pelvic pain scale has possible scores of 0 to 3, as outlined in Table 19.

Table 19: Subject Modified Biberoglu and Behrman Scales for Dysmenorrhea, Pelvic Pain, and Dyspareunia

Dysmenorrhea	Pelvic Pain	Dyspareunia	Numerical Score
No pain	No pain	No pain	0
Mild	Mild	Mild	1
Moderate	Moderate	Moderate	2
Severe	Severe	Severe	3
Did not Menstruate	--	No Intercourse	4

The mean sB&B for DYS during the Week 52, Week 104/EOT pain assessment period will be the average over the days when the DYS response was something other than "Did not menstruate." If the patient reports "Did not menstruate" for all days of the pain assessment period, then the mean sB&B score will be imputed as 0.

The mean sB&B for NMPP during the Week 52, Week 104/EOT pain assessment period, derived from the sB&B for pelvic pain, will be the average of the scores reported for days on which a patient reports she did not menstruate. Mean change of sB&B for NMPP and percent change from baseline will be presented by visit by treatment group.

The mean sB&B for dyspareunia during the Week 52, Week 104/EOT pain assessment period will be the average over the days when the dyspareunia response was something other than "No intercourse." Mean change of sB&B for dyspareunia and percent change from baseline will be presented by visit by pivotal phase 3 study treatment group. Additionally, the following will be summarized for patients who reported one or more day on which they had vaginal sexual intercourse during a given time interval; the percentage of patients whose maximum dysmenorrhea score was severe, moderate, mild, and none during the specified time interval; the percentage of patients whose maximum dysmenorrhea score was severe or moderate and mild or none during the specified time interval.

The mean change and percent change of sB&B score from baseline to Week 52, and to Week 104/EOT will be presented by visit and by the pivotal phase 3 study treatment group for DYS, NMPP, and dyspareunia separately. LS means of mean change and 95% CI are based on mixed-effects model with visit, pivotal phase 3 study treatment group, treatment-by-visit interaction, region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, >=5 years), and baseline value included as fixed effects. The multiple visits for each patient are the repeated measures as random effects within each patient, and an unstructured covariance

matrix is assumed. Here treatment refers to pivotal phase 3 study treatment group. Least squares mean and 95% CI will be presented by pivotal phase 3 study treatment group and by visit.

7.3.6. Patient Global Impression of Change

The PGICs completed by patients includes assessments of DYS, NMPP, and dyspareunia use a 7-point response scale. The following possible responses are: Much better, Better, A little better, The same, A little worse, Worse, or Much worse. The proportion of patients who are better or much better on the PGIC at Week 52 and two-sided 95% CI based on Clopper-Pearson exact binomial will be presented by pivotal phase 3 study treatment group for DYS, NMPP, and dyspareunia separately. Number and percentage of patients in summary of PGIC category will be presented by pivotal phase 3 study treatment group for DYS, NMPP, and dyspareunia separately.

7.4. Exploratory Efficacy Endpoints

Descriptive summaries by pivotal phase 3 study treatment group and mean change from baseline will be provided for the following exploratory endpoints.

For final analysis, the following exploratory endpoints will be assessed:

- Change from Baseline to Week 24, Week 52, Week 104 in the EHP-30 scale total score
- Change from Baseline to Week 24, Week 52, Week 104 in the EHP Work Domain score

  Change from Pivotal phase 3 Studies Baseline to Week 24, Week 52, Week 104 in the EQ-5D-5L

7.4.1. Exploratory Efficacy Analyses

EHP-30 Total Score

The total score for the EHP-30 questionnaire will be calculated and analyzed as a normalized score using the formula above. Total score will be summarized by visit by pivotal phase 3 study treatment group. Score change with 95% CI from pivotal phase 3 studies baseline to Week 24, Week 52, or Week 104 will be summarized by pivotal phase 3 study treatment group.

A mixed-effects model with repeated measures will be used to assess total score change for the EHP-30 at Week 24, Week 52 and Week 104. The model will have baseline value, visit, treatment, treatment-by-visit interaction, region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, >= 5 years) included as fixed effects. Visit is also included in the model as random effect within each patient and an unstructured variance-covariance matrix is assumed. If the mixed-effects model fails to converge, a first-order autoregressive variance-covariance matrix will be used. Here treatment refers to pivotal phase 3 study treatment group. Least squares mean and 95% CI will be presented by pivotal phase 3 study treatment group and by visit.

EHP Work Domain

The score for the 5-item EHP work domain questionnaire is calculated by adding the scores for

individual items (each with five response options scored from 0 to 4) to obtain a total raw score, then dividing by 20 and multiplying the result by 100 to obtain a normalized score that ranges from 0 to 100. The normalized score used for analysis is:

$$\text{Normalized score} = (\text{Total raw score} / 20) \times 100$$

Higher scores represent a greater (ie, more negative) impact of endometriosis on work-related activities. If one or more items are missing, then the score cannot be calculated for that patient and will be set missing.

The normalized score for the EHP-30 work domain will be summarized by visit and by pivotal phase 3 study treatment group. Score change from studies baseline to Week 24, Week 52, and Week 104 will be summarized by pivotal phase 3 study treatment group.

A mixed-effects model with repeated measures will be used to assess total score change for the EHP work domain at Week 24, Week 52 and Week 104. The model will have baseline value, visit, treatment, treatment-by-visit interaction, region (North America, Rest of World), time since initial surgical diagnosis of endometriosis (< 5, >= 5 years) included as fixed effects. Visit is also included in the model as random effect within each patient and an unstructured variance-covariance matrix is assumed. If the mixed-effects model fails to converge, a first-order autoregressive variance-covariance matrix will be used. Here treatment refers to pivotal phase 3 study treatment group. Least square means and associated 95% CIs will be presented by treatment and visit.

For each question, the proportion of patient in each category of the work domain will be presented at Baseline, week 24, Week 52 and Week 104 by pivotal phase 3 study treatment group. Additionally, the proportion of patients shifting from “often/always” to “never/rarely” from Baseline to Week 24, from Baseline to Week 52, and from Baseline to Week 104 will be described by visit and by pivotal phase 3 study treatment group.

European Quality of Life Five-Dimension Five-Level Scale

The EQ-5D-5L is a standardized instrument for use as a measure of health outcomes. Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on a 5-level categorical scale. The categorical changes of amount of improvement (1-4 categories), amount of deterioration (1-4 categories), or no change from baseline to Week 24, Week 52, and Week 104 will be summarized by pivotal phase 3 study treatment group. The EQ-5D-5L also has an assessment of overall health status that the patient rates on a 100-point visual analogue scale. The change from baseline to Week 24, Week 52, and Week 104 for the visual analogue scale scores will be summarized by pivotal phase 3 study treatment group.

8. PHARMACODYNAMIC ANALYSES

For pharmacodynamic assessment, data for the extension study consists of predose concentrations of serum estradiol. The change from the pivotal phase 3 study Baseline to Week 52 and to Week 104 in predose concentrations of serum estradiol will be summarized. This data will be listed and summarized using descriptive statistics (including raw and change from pivotal phase 3 study Baseline to Week 52 and Week 104 by pivotal phase 3 study treatment group, and by visit).

For pharmacodynamic assessment, the number and percentage of patients with individual E2 concentration values will be summarized by pivotal phase 3 study treatment group (relugolix + E2/NETA, relugolix + delayed E2/NETA, or placebo) and visit according to the following categories:

- < 10 pg/mL, 10 to < 20 pg/mL, 20 to < 30 pg/mL, 30 to < 40 pg/mL, 40 to < 50 pg/mL, 50 to < 60 pg/mL, 60 to < 70 pg/mL, and ≥ 70 pg/mL
- < 20 pg/mL, 20 to < 50 pg/mL, and ≥ 50 pg/mL
- < 20 pg/mL, 20 to < 60 pg/mL, and ≥ 60 pg/mL

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 extension study.

Safety assessments will include treatment-emergent adverse events, vital signs, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, mammograms (for women who are or become ≥ 40 years of age during the study), and endometrial biopsy.

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 affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the Schedule of Activities in the study protocol Section 1.1. Additionally, serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor regardless of causal relationship to study drug treatment.

Using a Safety Report Form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event 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, version 5.0 dated 27 Nov 2017), 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 pivotal phase 3 study drug.

Adverse event summaries will be based on treatment-emergent adverse events in the pivotal phase 3 and extension studies, unless otherwise specified. All adverse events in the pivotal phase 3 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;
  - Safety parameters of interest

  - Safety parameters of interest with first onset during extension study
- 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 (Day 1 to Week 24, > Week 24 to Week 52, >Week 52 to Week 78, > Week 78 to Week 104, > Week 104)), SOC and PT;
  - Exposure-adjusted AE rate by SOC and PT
- Adverse events reported in at least 5% of patients in any treatment group
  - By decreasing frequency of 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;
  - First onset events during extension study by decreasing frequency of PT
- Adverse events leading to study drug withdrawal;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Adverse events leading to dose withdrawal with first onset during extension study;
  - 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 SOC, PT and maximum grade
  - By decreasing frequency of PT;
  - 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.
  - First onset events during extension study by PT
  - Resolved while on study drug treatment (ie, prior to the last dose date)
- Adverse events with first onset during the extension study;
  - By SOC and PT;
  - By decreasing frequency of PT;
- Serious adverse events with first onset during the extension study;
  - By SOC and PT;
- Mood disorder event with first onset during the extension study;
  - By decreasing frequency of PT;
  - Resolved while on study drug treatment (ie, prior to the last dose date)
- Vasomotor symptoms with First Onset During the Extension Study
  - By SOC and PT;
  - By decreasing frequency of PT;
  - Resolved while on study drug treatment (ie, prior to the last dose date)
- Bone health related events
  - By decreasing frequency of PT;
  - First onset events during extension study by PT;
- Hepatic transaminase elevations
  - By decreasing frequency of PT;
  - First onset events during extension study by PT;
- Carbohydrate and lipid metabolic effects
  - By decreasing frequency of PT;
  - First onset events during extension study by 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 pivotal phase 3 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 pivotal phase 3 study or extension study;
- Deaths occurring after a patient leaves the extension study, or otherwise discontinues study drug, whether or not the patient completes the study to the nominal endpoint will be included in the analysis if death is reported prior to database lock date. Death reported after that will be saved in the database but will not be analyzed.

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 in a 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. Other Safety Parameters of Interest

In addition, other safety parameters of interest defined in Table 20 will be summarized by decreasing frequency of PT in the extension safety population. Additionally, event of uterine bleeding are summarized including MedDRA preferred terms: menorrhagia, metrorrhagia, menstruation irregular, vaginal haemorrhage, menometrorrhagia, polymenorrhoea, and uterine haemorrhage.

Table 20: Other Safety Parameters of Interest

Grouping	Search Criteria
Bone health related 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 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 = Standardized 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 pivotal phase 3 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 pivotal phase 3 studies and extension study.

9.1.9. Adverse Events of Clinical Interest

Adverse Events of clinical interest in the pivotal phase 3 studies and the extension study are defined as any increase in ALT or AST $\geq$ 3 x ULN, which are reported as "Yes" for adverse events of clinical interest in the adverse event CRF. Adverse events of clinical interest will be summarized by PT.

9.2. Laboratory Data

Laboratory parameters, including chemistry and hematology panels, and hormonal tests specified as per protocol for the pivotal phase 3 and extension studies, and collected from the central laboratory will be tabulated and presented in by-patient listings. Except for the tables using pre-defined threshold for chemistry and hematology parameters, local laboratory parameters will not be presented in tables. The local laboratory parameters will be presented in by-patient listings. Urinalysis and hepatitis virus serological test results will be provided in by-patient listing only.

For patients with incomplete recovery of bone mineral density loss at the 6- and 12-month post-treatment Follow-Up visit, clinical laboratory tests specified in the protocol should be performed. These laboratory assessments will be submitted to the central laboratory. If these laboratory assessments are scheduled to occur after the study database is locked, they will be performed at a local laboratory.

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 (ie, low and high) if she has laboratory values meeting each criterion. Shift tables will be provided for each parameter gradable by the CTCAE to summarize Baseline toxicity grade versus worst post-Baseline toxicity grade throughout the pivotal phase 3 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 pivotal phase 3 and extension studies. A shift table for selected parameters based on predefined categories will be provided to summarize baseline category versus post-baseline category at Week 104. The parameters include glucose (< 100 mg/dL, 100 - 125 mg/dL, 126 - 200 mg/dl, > 200 mg/dL), fasting glucose (< 100 mg/dL, 100 - 125 mg/dL, 126 - 200 mg/dl, > 200 mg/dL), HbA1c (<= 5.6%, 5.7% - 6.4%, 6.5% - 8.0%, 8.1% - 9.4%, 9.5% - 11%, > 11%), low density cholesterol (normal <100 mg/dL, normal high 100 to < 130 mg/dL, borderline high 130 to < 160 mg/dL, high 160 to < 190 mg/dL, very high >= 190 mg/dL), high density cholesterol (< 40 mg/dL, 40 - 59 mg/dL, >= 60 mg/dL), triglycerides (< 150 mg/dL, 150 - 300 mg/dL, 301 - 500 mg/dL, 501 - 1000 mg/dL, > 1000 mg/dL) and total cholesterol (<= ULN, > ULN - 300 mg/dL, > 300 - 400 mg/dL, > 400 - 500 mg/dL, > 500 mg/dL).

Boxplots of laboratory values over time, including visits in both the pivotal phase 3 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, estimated 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 pivotal phase 3 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 pivotal phase 3 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 21. The number and percentage of patients with concurrent (defined as measurements on the same day) ALT or AST $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN, Concurrent ALT or AST $\geq 3 \times$ ULN and total bilirubin $> 2 \times$ ULN and ALP $< 2 \times$ ULN will also be presented. A by-patient listing will also be provided,

Table 21: 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	Concurrent ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
ALT or AST, total bilirubin, and ALP	Concurrent ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

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

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 2)**Error! Reference source not found.** by pivotal phase 3 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 pivotal phase 3 studies 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 and central reader interpretation and diagnoses will be presented in by-patient listings.

9.3.2. Vital Signs

Blood pressure (systolic and diastolic), heart rate, and BMI will be summarized at pivotal phase 3 study Baseline and each subsequent scheduled assessment, including visits in both the pivotal phase 3 study and extension study, by pivotal phase 3 study treatment group. Change from pivotal phase 3 study 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 22, 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 22: Categories of Potentially Clinically Significant Abnormalities in Vital Signs

Parameter	Category
Systolic blood pressure	≥ 140 mmHg over 2 consecutive visits ≥ 180 mmHg over 2 consecutive visits ≤ 90 mmHg over 2 consecutive visits
	≥ 140 mmHg and > highest screening or baseline in pivotal phase 3 studies over 2 consecutive visits; ≥ 180 mmHg and > highest screening or baseline in pivotal phase 3 studies over 2 consecutive visits
	≤ 90 mmHg and < lowest screening or baseline in pivotal phase 3 studies over 2 consecutive visits
	Increase of ≥ 20 mmHg from Baseline in pivotal phase 3 studies over 2 consecutive visits Decrease of ≥ 20 mmHg from Baseline in pivotal phase 3 studies over 2 consecutive visits
Diastolic blood pressure	≥ 90 mmHg over 2 consecutive visits ≥ 105 mmHg over 2 consecutive visits ≤ 50 mmHg over 2 consecutive visits
	≥ 90 mmHg and > highest screening or baseline in pivotal phase 3 studies over 2 consecutive visits ≥ 105 mmHg and > highest screening or baseline in pivotal phase 3 studies over 2 consecutive visits
	≤ 50 mmHg and < lowest screening or baseline in pivotal phase 3 studies over 2 consecutive visits
	Increase of ≥ 15 mmHg from Baseline in pivotal phase 3 studies over 2 consecutive visits Decrease of ≥ 15 mmHg from Baseline in pivotal phase 3 studies over 2 consecutive visits
Heart rate	≥ 120 bpm and > highest screening or baseline in pivotal phase 3 studies over 2 consecutive visits
	< 45 bpm and < lowest screening or baseline in pivotal phase 3 studies over 2 consecutive visits
	Increase of ≥ 15 bpm from Baseline in pivotal phase 3 studies over 2 consecutive visits Decrease of ≥ 15 bpm from Baseline in pivotal phase 3 studies over 2 consecutive visits

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

9.3.3. Endometrial Biopsy

The protocol-specified endometrial biopsy procedure was performed at Baseline for all patients in MVT-601-3101 and MVT-601-3102, and at the pivotal phase 3 study Week 24/ET visit for all patients who participated in MVT-601-3101 only. Starting from protocol amendment 2.0, endometrial biopsy procedure was required for all patients in the extension study at Week 52 and Early Termination Visit (except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy). However, the procedure may have been done if it would aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 was recommended for all patients who complete the open-label extension; however, patients have the option to opt out. Consensus readings by independent pathologists were performed on all endometrial biopsies.

The Week 52, Week 104, and Early Termination endometrial biopsy samples will be submitted to the central laboratory. If the Week 52, Week 104, or Early Termination biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required. No further action is required for endometrial thickness ≤ 5 mm. Repeat endometrial sampling will be collected for endometrial thickness > 5 mm at any location or any other endometrial abnormality is present. Unscheduled endometrial biopsies may also be performed when medically indicated and as deemed necessary by the investigator.

Endometrial biopsies will be summarized using frequencies and percentages according to primary diagnosis and secondary diagnosis from the consensus reading (Table 23). Primary and secondary diagnosis from consensus reading evaluation are summarized Table 23 Endometrial biopsies performed in the pivotal phase 3 studies and extension study will be summarized by pivotal phase 3 study treatment group and by visit. Any repeat endometrial biopsies performed will also be summarized. Biopsy reported in the pivotal study CSRs will be excluded from the extension study analyses. All endometrial biopsy findings and transvaginal ultrasound data will also be provided in a by-patient listing, including visits in both the pivotal phase 3 study and extension study.

Table 23: Categories of Primary Diagnosis in Endometrial Biopsies

Primary Diagnosis Category	Secondary Diagnosis
Normal-Proliferative	• Weakly proliferative • Proliferative • Disordered proliferative
Normal-Secretory/Menstrual/Mixed	• Secretory • Menstrual • Progestational/Decidualized • Mixed
Normal-Atrophic/Indeterminate/Inactive	• Atrophic • Indeterminate/Inactive

Hyperplasia	• Simple hyperplasia without atypia • Simple hyperplasia with atypia • Complex hyperplasia without atypia • Complex hyperplasia with atypia
Carcinoma	–
Inadequate	–
Missing	–
Additional Diagnosis (Other reported findings)	• Reactive/Inflammatory • Polyp • Metaplasia • Glandular and/or Stromal Breakdown

9.3.4. Mammogram

A requirement for post-treatment mammograms was added starting with protocol amendment 3.0 as follows: For women who are or become ≥ 40 years old at the time of the visit, the protocol-specified local mammogram was to be performed at Week 52 or at Week 104/Early Termination. If a patient had a recent mammogram per standard of care within the six months before Week 52 that was Breast Imaging Reporting and Data System category 1 or 2 or equivalent or had benign findings, as determined by the investigator or medical monitor, a mammogram is not required at Week 52 but should be completed by Week 104/Early Termination. If a patient turns 40 years old after the Week 52 visit has occurred, a mammogram should be performed no later than the Week 104/Early Termination visit. All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent and recorded in the eCRF.

Mammograms performed in the extension study at Week 52, Week 104//Early Termination will be summarized. Number and percentage of patients in each Breast Imaging Reporting and Data System category or equivalent will be summarized by visit and by pivotal phase 3 study treatment group. Mammogram data will also be provided in a by-patient listing in the extension study.

9.3.5. Bone Mineral Density

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

BMD measured at Baseline and post-baseline visits will be summarized descriptively by pivotal phase 3 study treatment group and each measured anatomical location for all patients in the Extension Safety population. Mean change and percentage changes from baseline along with 95% CIs will be summarized by pivotal phase 3 study treatment group, visit and anatomical location. Percentage change from baseline with its corresponding 95% CI will be plotted by

visit, pivotal phase 3 study treatment group, and anatomical location. Percentage change from Week 12 to subsequent visits along with 95% CIs will be summarized by pivotal phase 3 study treatment group, visit and anatomical location.

A mixed-effects model with repeated measures will be used to assess BMD at each visit. The model will have age at Baseline, treatment, visit, treatment-by-visit interaction, Baseline BMD value, stratification factors (geographic region and time since initial surgical diagnosis), body mass index at baseline, race (Black/African American versus Other) as fixed effects using an unstructured variance-covariance matrix. If the mixed-effects model fails to converge, a first-order autoregressive variance-covariance matrix will be used. Here treatment refers to pivotal phase 3 study treatment group. Least squares mean on each anatomical location will be presented and plotted by pivotal phase 3 study treatment group at each visit with associated 95% CIs. Specifically for percentage change from Week 12 to subsequent visits, week 12 BMD value is considered as a baseline.

Categorical representation of percentage change from Baseline to post-baseline visits will be presented by the number and proportion of patients who had BMD increased (> 0%), no change (= 0%) and decreased by < 2%, >= 2% to 3%, > 3% to 5%, > 5% to 8%, and > 8% by pivotal phase 3 study treatment group and anatomical location. The 95% CIs will be provided for the respective proportions. The number and percentage of patients meeting a bone mineral density decrease of at least 4%, 5%, 6%, 7%, or 8% by anatomical location (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the pivotal phase 3 study treatment group.

Categorical changes from Baseline in overall BMD (defined as lumbar spine and total hip) also will be assessed at post-baseline visits. 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 pivotal phase 3 study treatment group, visit, and anatomical location with descriptive statistics including 95% CIs. Number and percentage of patients with a Z -score < -2.0 will be presented by pivotal phase 3 study treatment group, visit, and anatomical location. Number and percentage of patients with a Z score- change from baseline >= 0, < 0 to -0.25, < -0.25 to -0.5, < -0.5 to -0.75, < -0.75 to -1.0, < -1.0 to -2.0 and < -2.0 will be presented by pivotal phase 3 study treatment group and anatomical location at Week 24, Week 52 and Week 104.

BMD change from baseline in the category of decreased, no change, and increased will be presented by pivotal phase 3 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 24.

Table 24: Planned Subgroup Analyses

Subgroup Name	Subgroup Level

Geographic region	North America, Rest of World
Age category (years)	< 35, ≥ 35
Race	Black or African American, Other
Ethnicity	Hispanic or Latino, Not Hispanic or Latino
BMI (kg/m^2) at Baseline	< 25, ≥ 25

Abbreviations: BMI = body mass index. For patients reporting multiple races, those who reported "Black/African-American" as one of the races will be included in the "Black or African-American" category.

Post-treatment BMD

Determination of bone mineral density by DXA at post-treatment follow-up of findings will proceed according to the rules defined by original protocol or amendments. Complete data collected during the post-treatment Follow-Up period will be summarized and reported in an addendum to the final clinical study report.

Patients required to have post-treatment follow up for BMD are defined according to the rules defined in section 2.1 (Table 2):

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. Summary statistics will be provided for post-treatment DXA by anatomic location at 6 months and 12-months. Summary of BMD loss recovery during post treatment follow up will be provided by location and by pivotal phase 3 study treatment group. Summaries will be presented of percent change in BMD from baseline for patients who entered post-treatment follow-up period by anatomic location and by pivotal phase 3 study treatment group. For patients who decline to participate in the 6-month and 12-month PTFU, reasons of decline will be summarized in the by-patient listing.

Post-treatment follow-up medical and gynecological history, concomitant medications, and bone fracture events will be listed in the by-patient listing.

For patients with PTFU scans showing a bone loss of ≥ 3% at the lumbar spine and/or total hip at the 6-month and 12-month PTFU visit compared with the pivotal study baseline, clinical laboratory evaluations including vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous will be listed in the by-patient listings.

9.3.6. Menstruation Recovery

Status of menstruation recovery will be documented at the Follow-Up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted again by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.

Menstruation recovery data will be presented in the table by pivotal phase 3 study treatment group for patients in the Extension Study Population. The table will include menstruation status during follow up, number of days to return of menses from last dose of study drug, and

explanation for the lack of menstruation resumption. Menstruation recovery data will also be provided in a by-patient listing,

9.3.7. Analysis of Bleeding Profiles

Bleeding profile categories will be determined based on the amount of bleeding experienced by patients as reported in the eDiary. When a patient is menstruating, the amount of bleeding during the past 24 hours is captured daily in the eDiary with five response options: spotting, light, moderate, heavy, and extremely heavy. It will be assumed that there is no bleeding on days that the patient either uses the eDiary and reports that she is not menstruating, or when the patient misses reporting menstruating within eDiary cycle. The responses to the eDiary question about the amount of bleeding will be used to define the bleeding profile categories (Table 25).

After Week 52, to reduce patient burden, eDiary data were collected over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit. After the Week 104 visit, patients continued daily eDiary entry until the 30-day Follow-Up visit.

Table 25: Definitions of Bleeding Profile Categories

Bleeding Profile Category	Category Definition
Irregular bleeding	3 to 5 bleeding/spotting episodes and less than 3 bleeding-free intervals of least 14 days during a bleeding-profile period
Prolonged bleeding	Bleeding/spotting episodes of more than 14 days during a bleeding-profile period
Frequent bleeding	More than 5 bleeding/spotting episodes during a bleeding-profile period
Infrequent bleeding	1 or 2 bleeding/spotting episodes during a bleeding-profile period
No bleeding	No bleeding during a bleeding-profile period
Normal bleeding	None of the above definitions are met

[a] Bleeding/spotting episode: at least one day with bleeding or spotting reported, bounded by bleeding-free intervals.
[b] Bleeding-free interval: at least two consecutive days with no bleeding or spotting reported, bounded by bleeding/spotting episodes.

The number and percentage of patients belonging to each of the bleeding profile categories defined in Table 25 will be summarized by pivotal phase 3 study treatment group over four bleeding-profile periods: Days 1 through 90, Day 91-Day 180, Day 181-Day 270, and Day 271-365. A patient must have at least 90 days of treatment exposure to be included in the summary of each period. No analyses of bleeding profile after Day 365 will be performed because all of the eDiary reporting cycles are less than 90 consecutive days.

Summaries of bleeding intensity and number of bleeding days based on 28-day intervals will be provided from the last 28 days starting from the pivotal phase 3 baseline through Day Day 731. The following 28-day windows will be used for summaries of bleeding during the randomized treatment period: Week 4 (Days 1 through 28), Week 8 (Days 29 through 56), Week12 (Days 57 through 84), Week 16 (Days 85 through 112), Week 20 (Days 113 through 140), Week 24 (Days 141 through 168, Week 28 (Days 169 through 196), Week 32 (Days 197 through 224), Week 36 (Days 225 through 252), Week 40 (Days 253 through 280), Week 44 (Days 281 through 308), Week 48 (Days 309 through 336), Week 52 (Days 338 through 365), Week 65

(Days 429 through 456), Week 78 (Days 520 through 547), Week 91 (Days 611 through 638) and Week 104 (Days 704 through 731). Only patients who were on study drug for all days in a given 28-day window will be included in the summary for that window. The specific summaries of bleeding that will be provided are described in Table 26.

Table 26: Summaries of Bleeding Amount and Number of Bleeding Days

Bleeding outcome	Type of summary
Bleeding amount (or intensity), defined numerically as: Spotting = 1 Light = 2 Moderate = 3 Heavy = 4 Extremely Heavy = 5	Mean, SD, median, minimum, maximum; based on all eligible patients who report bleeding in the eDiary.
Number of bleeding days	Mean, SD, median, minimum, maximum; based on all eligible patients, regardless of whether any bleeding is reported in the eDiary.
Number of bleeding days by the following bleeding amount (or intensity) categories: No bleeding Spotting Light Moderate Heavy Extremely Heavy	Mean number of days per category.

9.3.8. Amenorrhea Rate and Sustained Amenorrhea Rate

Determination of amenorrhea will be based on a patient's daily menstruation status as reported in the eDiary. Amenorrhea for at least 56 consecutive days is defined as the lack of bleeding for at least 56 consecutive days after starting randomized study treatment in pivotal phase 3 study until Week 52. Amenorrhea for at least 28 consecutive days is defined as the lack of bleeding for at least 28 consecutive days after starting randomized study treatment in pivotal phase 3 study until Week 104. The study day when amenorrhea begins is defined as the first study day following the last reported day of menstruation. It will be assumed that there is no menstruation on days when menstrual status is not reported in the eDiary.

A summary of amenorrhea for at least 56 consecutive days will be provided by pivotal phase 3 study treatment group based on the following 56-day time intervals from pivotal phase 3 baseline through Day 365: Week 8 (Days 1 through 56), Week 12 (Days 29 through 84), Week 16 (Days 57 through 112), Week 20 (Days 85 through 140), Week 24 (Days 113 through 168), Week 28 (Day 141 through 196), Week 32 (Day 169 through 224), Week 36 (Day 197 through 252), Week 40 (Day 225 through 280), Week 44 (Day 253 through 308), Week 48 (Day 281 through 336), and Week 52 (Day 310 through 365). No analyses of 56-day amenorrhea after

Week 52 will be performed because some eDiary reporting cycles are less than 56 days. A summary of amenorrhea for at least 28 consecutive days intervals from pivotal study baseline through Day 731 will be provided by pivotal phase 3 study treatment group. The number and percentage of patients who are amenorrheic (ie, the amenorrhea rate) in each time interval will be presented. In each time interval, the numerator for the amenorrhea rate is the number of patients who did not bleed during the time interval; the denominator is the number of patients who remained on treatment during the entire time interval.

Sustained amenorrhea through week 52, defined as lack of bleeding for at least 56 days that continues until the Week 52 visit or the date of last dose of extension study treatment for early terminated patients who terminated before Week 52, will be summarized by pivotal phase 3 study treatment group in the time intervals defined above. No analyses of sustained amenorrhea after Week 52 will be performed because some eDiary reporting cycle were less than 56 days. In each time interval, the number and percentage (ie, the sustained amenorrhea rate) of patients with sustained amenorrhea will be presented. In each time interval, the numerator of the sustained amenorrhea rate will be the number of patients with sustained amenorrhea beginning on or prior to the end of the time interval; the denominator will be the number of patients in the Extension Safety population. For patients who discontinued early, their amenorrhea status at the time of discontinuation will be carried forward until Week 104.

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

11. REVISION HISTORY

Version	Effective Date	Description of Changes

APPENDICES

Appendix 1. Protocol-Specified Rescue Analgesics

The medications below are listed based on their dose strength. The protocol stated that the prescription (or instructions for use) for these medications may allow for use of more than one tablet at any given time. Additionally, analgesics were to be prescribed in accordance with the respective country's approved product labeling and the subject's historical use of opioid analgesics should be taken into consideration when prescribing these drugs.
Only one Tier 2 medication was allowed to be selected for a given patient to be used throughout the study and this was to be the same Tier 2 medication used in the pivotal phase 3 study.

Study-specified analgesics were as follows:

- Tier 1
  - ibuprofen (200 mg dose strength)[1]
- Tier 2
  - tramadol (37.5 mg) / paracetamol (325 mg)
  - tramadol (50 mg)
  - codeine (30 mg)
  - codeine (30 mg) / paracetamol (300 mg)
  - codeine (30 mg) / paracetamol (500 mg)
  - codeine 15 mg/ paracetamol (500 mg)
  - hydrocodone (5 mg) / acetaminophen 325 mg

Within a given country, the choice of Tier 2 analgesic was limited to one or two of the above Tier 2 analgesic medications.

Appendix 2. 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	eGFR < 15 mL/min per 1.73 m^2
CR > 50% increase from BL	eGFR ≥ 15 to < 30 mL/min per 1.73 m^2
	eGFR ≥ 30 to < 60 mL/min per 1.73 m^2
	eGFR ≥ 60 to < 90 mL/min per 1.73 m^2
	eGFR ≥ 90 mL/min per 1.73 m^2

Metabolic Parameters	
Glucose, Fasting Glucose	Highest Postbaseline Glucose
< 100 mg/dL at BL	Gluc ≥ 200 mg/dL and > BL
< 100 mg/dL	Gluc ≥ 200 mg/dL and ≥ 126 mg/dL at BL
≥ 100 to < 126 mg/dL	Gluc ≥ 500 mg/dL and > BL
≥ 126 mg/dL	Gluc ≥ 500 mg/dL and ≥ 126 mg/dL at BL
≥ 100 to < 126 mg/dL at BL	
< 100 mg/dL	
≥ 100 to < 126 mg/dL	
≥ 126 mg/dL	
≥ 126 mg/dL at BL	
< 100 mg/dL	
≥ 100 to < 126 mg/dL	
≥ 126 mg/dL	
Lipids	
Total CHOL > 200 mg/dL and > BL	HDL < LLN and < BL
Total CHOL increase > 30 mg/dL from BL	
Total CHOL Normal < 200 mg/dL	LDL > ULN and > BL
Total CHOL Borderline High 200 to < 240 mg/dL	LDL 100 - < 130 mg/dL and > BL
Total CHOL High >= 240 mg/dL	LDL 130 - < 160 mg/dL and > BL
	LDL 160 - < 190 mg/dL and > BL
TRIG > ULN and > BL	LDL >= 190 mg/dL and > BL
TRIG 150 - < 200 mg/dL and > BL	
TRIG 200 - < 500 mg/dL and > BL	LDL Normal < 100 mg/dL
TRIG >= 500 mg/dL and > BL	LDL Normal high 100 - < 130 mg/dL
	LDL Borderline High 130 - < 160 mg/dL
	LDL High 160 - < 190 mg/dL
	LDL very high >= 190 mg/dL
Electrolytes and other Chemistry Parameters	
ALB < LLN and < BL	MG < LLN and < BL
ALB > ULN and > BL	MG > ULN and > BL
ALP > 2 × ULN and > BL	CK > 2 × ULN and > BL

ALP > 5 × ULN and > BL	CK > 5 × ULN and > BL
ALP > 10 × ULN and > BL	CK > 10 × 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 ≤ 5.6% and > BL
MONO < LLN and < BL	HbA1c 5.7 - 6.4% and > BL
MONO > ULN and > BL	HbA1c ≥ 6.5% and > BL
	HbA1c increase > 1.0% from BL
HbA1c < 5.7%	HbA1c < 5.7%

HbA1c 5.7 - 6.4%	HbA1c 5.7 - 6.4%
HbA1c 6.5 – 8.0%	HbA1c ≥ 6.5%
HbA1c 8.1 - 9.4%	
HbA1c 9.5 - 11%	
HbA1c > 11%	

Abbreviations: ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BASO = basophils; BILI = bilirubin; BL = baseline; CA = calcium; CHOL = cholesterol; CK = creatine kinase; CR = creatinine; E2 = estradiol; EOS = eosinophils; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; Gluc = glucose; HbA1c = hemoglobin A1c; HCT = hematocrit; HDL = high density lipoprotein cholesterol; HGB = hemoglobin; K = potassium; LDL = low density lipoprotein cholesterol; LLN = lower limit of normal; LYM = lymphocytes; MCV = mean corpuscular volume; MG = magnesium; MONO = monocytes; NA = sodium; NETA = norethindrone acetate; NEUT = neutrophils; PHOS = phosphate; PLT = platelets; TRIG = triglycerides; ULN = upper limit of normal; WBC = white blood cell.

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