16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Original

Protocol Amendment 1

Protocol Amendment 1 Summary of Changes

CLINICAL STUDY PROTOCOL

Study Title:	An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix Co-administered with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-035
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 CH-4051 Basel Switzerland
Regulatory Identifier(s):	Eudra CT # 2018-001368-43 IND # 131161
Version and Effective Date:	Draft: Original Effective: 11-July-2018

SPONSOR SIGNATURE PAGE

An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix Co-administered with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-035

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

10-July-2018
Date

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SPONSOR SIGNATURE PAGE

An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix Co-administered with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

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11 Jul 2018
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11 Jul 2018
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	Body Mass Data
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dihyroepiandrosterone
DXA	dual-energy x-ray absorptiometry
E2/NETA	estradiol 1.0 mg/norethindrone acetate 0.5 mg
ECG	electrocardiogram
eCRF	electronic case report form
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HMB	heavy menstrual bleeding
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MBL	menstrual blood loss
mITT	modified Intent-to-Treat
OLE	Open-label extension; LIBERTY EXTENSION; MVT-601-3003
PD	pharmacodynamic
PGA	Patient Global Assessment
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT Interval Corrected by the Fridericia Correction Formula
RBC	red blood cell
SF-36	Short Form (36)
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
WPAI-UF	Work Productivity Activity Impairment-Uterine Fibroids
ULN	Upper limit of normal
US	United States
WBC	white blood cells
WPAI-UF	Work Productivity Activity Impairment-Uterine Fibroids

1. PROTOCOL SYNOPSIS

Study Title	An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-035
Location	Multinational, including North and South America, Europe, and South Africa
Study Centers	Approximately 240 sites
Study Phase	Phase 3
Target Population	Women 18 to 51 years old diagnosed with uterine fibroids who complete the open-label extension study MVT-601-3003 (OLE study) and who meet the definition of responder. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.
Number of Patients Planned	Approximately 360

Study Objectives	In women with uterine fibroids who complete the OLE study and are identified as responders, the efficacy objectives are as follows:
	<u>Primary Efficacy Objective</u>
	• To evaluate the long-term effect of relugolix 40 mg with estradiol 1.0 mg and norethindrone acetate 0.5 mg (relugolix with E2/NETA) once daily, compared with placebo on menstrual blood loss at Week 76 (24 weeks after randomization).
	<u>Secondary Efficacy Objectives</u>
	• To evaluate the long-term effect of relugolix with E2/NETA once daily, compared with placebo on menstrual blood loss at 52-weeks after randomization.
	• To evaluate the effect of retreatment with relugolix with E2/NETA on menstrual blood loss in patients whose menstrual blood volume returned to ≥ 80 mL during the 52-week randomized period.
	• To evaluate the long-term effect of relugolix with E2/NETA at 52 weeks after randomization on the following:
	  • Achievement of amenorrhea
	  • Resumption of menses
	  • Resumption of heavy menstrual bleeding (HMB)
	  • Hemoglobin
	  • Health-related quality of life as measured by the Short Form (36) (SF-36)
	  • Patient Global Assessment (PGA) for function and symptoms
	  • Work and productivity impact as measured by the Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF)

	• Disease-specific quality of life as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL). <u>Pharmacodynamic Objectives</u> • To characterize the pharmacodynamic (PD) effect of withdrawal from relugolix with E2/NETA. <u>Safety Objectives</u> • To evaluate the safety and tolerability of relugolix with E2/NETA once daily for up to an additional 52 weeks, in patients who previously completed (responders and partial responders) the OLE study. • Adverse events • Changes in bone mineral density.

Study Design

Overall Study Design: This is an international phase 3 double-blind, placebo-controlled, Randomized Withdrawal study that will enroll eligible patients with uterine fibroids who have completed the 24-week treatment period in a Parent study (study MVT-601-3001 or study MVT-601-3002) and the 28-week treatment period of the OLE (MVT-601-3003) study. When including treatment during the Parent study and the OLE study, patients completing this Randomized Withdrawal study will have received up to a total of 104 weeks of treatment.

Study Population: All patients who complete the OLE study with a response to treatment, provide informed consent, and met all eligibility criteria for study MVT-601-035 will be eligible to participate. Approximately 360 women (responders) with heavy menstrual bleeding associated with uterine fibroids will be enrolled. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.

Objectives: The objectives of the study are to evaluate long-term efficacy and safety of treatment with relugolix with E2/NETA for up to 104 weeks (total treatment duration includes the Parent study, OLE study, and Randomized Withdrawal study).

Treatment Assignment

Approximately 360 patients completing the OLE study and meeting the definition of responder and meeting all other eligibility criteria will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA or placebo, once daily, for up to 52 weeks. Stratification variables will include geographic region (North America vs Europe vs Latin America vs Rest of World), duration of relugolix exposure prior to randomization (28 weeks vs 52 weeks), and baseline menstrual blood loss volume in the Parent study (< 225 mL vs ≥ 225 mL). For patients whose menstrual bleeding returns to ≥ 80 mL (heavy menstrual bleeding), treatment with open-label relugolix with E2/NETA (latter also referred to as "add-back" in context of hormonal "add-back") will be restarted. A Schedule of Activities is provided in Table 1-1.

Screening and Baseline Procedures: The study consists of a screening period and a treatment period (randomized or open-label) of up to 52 weeks. Screening and baseline procedures will be done at the same visit for this Randomized Withdrawal study (referred to as the "Week 52/Baseline visit" in this study), which coincides with the Week 52 visit of the OLE study and will be defined as the date of completion of the last procedure in the OLE study (see Schedule of Activities; Table 1-1). The Week 52/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, transvaginal ultrasound, and endometrial biopsy (only if required). When Week 52/Baseline procedures in the OLE study have been completed, the investigator will assess patient eligibility for participation in this study. The eligibility assessment will be based on data available at the Week 52/Baseline visit. No study

procedures will be performed until the consent form is signed. Patients will receive their last dose of study drug in the OLE study on the day of the Week 52/Baseline visit (as per the OLE study protocol). Following confirmation that the patient is eligible for this Randomized Withdrawal study and has provided informed consent to participate, the patient will be provided blinded study drug to begin dosing the following day. The first dose of study drug will be self-administered the next morning following the Week 52/Baseline visit.

Post-baseline Procedures: Study participants will be randomized to take either blinded study treatment (relugolix with E2/NETA or placebo) orally once daily or, when retreatment is indicated, open-label relugolix with E2/NETA for up to additional 52 weeks (beyond the 52 weeks of previous treatment during the Parent/OLE studies). All post-baseline procedures are provided in the Schedule of Activities (Table 1-1). Patients will be contacted on Week 52/Day 1 to confirm initiation of self-administered dosing.

Patients will be asked to provide feminine products for alkaline hematin analysis at each visit. If the analysis confirms return of heavy menstrual bleeding (defined as menstrual blood loss of ≥ 80 mL) the patient will be offered retreatment with open-label relugolix with E2/NETA with the onset of the next menses. They will resume collection of feminine products for alkaline hematin analysis until two consecutive analyses confirm resolution of heavy menstrual bleeding (menstrual blood loss of < 80 mL). Patients will complete the bleeding diary daily including compliance with study drug, vaginal bleeding, and use of feminine products.

Safety will be assessed throughout the study by monitoring adverse events, vital signs and weight, physical examinations, clinical laboratory tests, and bone mineral density with dual-energy x-ray absorptiometry (DXA). Quality of life questionnaires will be completed according to the Schedule of Activities (Table 1-1). There is a Safety Follow-up visit (approximately 30 days after last dose of study drug) for all patients, and additional unscheduled follow-up visit(s) may be arranged at any time during the study for patients with study-related safety concerns, as needed.

The PD effect of withdrawal from relugolix with E2/NETA will be characterized by measuring the pre-dose concentration of estradiol at Week 56.

Status of menstruation recovery will be documented at the Safety Follow-up visit (30 days after last dose of study drug). Patients whose menses have not resumed as of the Safety Follow-up visit and for whom there is no explanation for the lack of resumption (e.g., medical procedure or medications) will be contacted again by telephone 12 (± 2) weeks after the Safety Follow-up visit to determine if menses have resumed. These patients will be asked about factors that may affect resumption of menses.

If a patient enrolls directly into another relugolix clinical study upon completion of the Week 104/Early Termination visit, then the Safety Follow-up visit, and the follow-up procedures performed under this protocol may be waived.

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria are met at the time of the Week 52/Baseline visit:

1. Completed the OLE study;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-035;

   Note: Procedures conducted as part of the OLE study that also serve as baseline procedures for this study may be done under the informed consent for the OLE study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including the Safety Follow-up period;

4. Is a responder: Has a menstrual blood loss of < 80 mL AND at least a 50% reduction from the Parent study baseline based on the results of the alkaline hematin testing performed on the feminine products returned at the Week 48 visit of the OLE study. Results from Week 44 may be used if Week 48 data is unavailable;
5. Has a negative urine pregnancy test at the Week 52/Baseline visit;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the treatment period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 24 weeks prior to the Week 52/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 16 weeks prior to the Week 52/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (e.g., Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study:

1. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the Parent study or OLE study;
2. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (e.g., bilateral hip replacement or spinal hardware in the lumbar spine);
3. Anticipates use of any prohibited medications as detailed in Section 5.9.1;
4. Has developed any contraindication to treatment with estradiol or norethindrone acetate including:
   a. Known or suspected breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism;
   d. Active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. Porphyria;
5. Has current active liver disease from any cause;
6. Has a new diagnosis of a systemic autoimmune disease (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic

arthritis, vasculitic syndromes, etc.). Psoriasis not requiring or anticipated to require systemic therapy is permitted; 7. Had any of the following clinical laboratory abnormalities at the OLE study Week 48 visit or any subsequent visit: a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome); c. Hemoglobin < 8 g/dL despite iron supplementation; 8. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 4 weeks after the last dose of study drug, or plans to donate ova during the study period or within 8 weeks after the last dose of study drug; 9. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor; 10. Met a withdrawal criterion in the OLE study.	
Dose and Route of Administration	Test Product Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The hormonal add-back therapy will be over-encapsulated. Reference Product Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active hormonal add-back therapy in size, shape, and color. Open-label Product Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. Study treatment will be self-administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 52 weeks.
Criteria for Evaluation	Inferential efficacy assessments will be made on data observed from Week 52 to Week 104 between the following two study treatment groups: • Group A: 52 weeks of oral relugolix with E2/NETA, once daily; • Group B: 52 weeks of placebo relugolix plus capsule of placebo estradiol/norethindrone acetate. Week 52 of the OLE study will define the Baseline for this Randomized Withdrawal study and will be used as the reference point for all changes from baseline-related endpoints. The menstrual blood loss (MBL) volume at the Week 52 period of the OLE study will establish the patient's baseline for evaluation of menstrual blood loss during the 52-week randomized treatment period of this Randomized Withdrawal study.

	Primary Efficacy Endpoint • Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the randomized treatment period) as measured by the alkaline hematin method. Secondary Efficacy Endpoints • Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 104 (Week 52 of the randomized treatment period) as measured by the alkaline hematin method; • Change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period); • Percentage change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period); • Proportion of patients who responded (menstrual blood loss volume of < 80 mL) to retreatment with relugolix with E2/NETA during the retreatment period among placebo patients whose menstrual blood volume had returned to ≥ 80 mL during the 52-week randomized treatment period. The following secondary endpoints will be assessed at Week 76 and at Week 104 during the randomized treatment period: • Proportion of women achieving or maintaining amenorrhea; • Proportion of women whose menses has resumed (among those who were amenorrhoeic at Week 52/Baseline); • Time to resumption of menses; • Proportion of women with menstrual blood volume ≥ 80 mL at any timepoint during the 52-week randomized treatment period; • Time to resumption of menstrual blood volume ≥ 80 mL; • Change from Week 52/Baseline in hemoglobin; • Change from Week 52/Baseline in SF-36 domain and summary component scores; • Change from Week 52/Baseline in PGA for function and symptoms score; • Change from Week 52/Baseline in the WPAI-UF scores; • Change from Week 52/Baseline in the Uterine Fibroid Scale Quality of Life (UFS-QoL) Symptom Severity scale, and sub-scale scores and total scores. Pharmacodynamic Endpoint • Pre-dose concentration of estradiol at Week 56. Safety Endpoints • Incidence of adverse events, change in vital signs and clinical laboratory tests; • Percent change from Week 52/Baseline to Week 104 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.
Statistical Methods	
Efficacy The primary efficacy endpoint of the study is the proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the randomized treatment period) as measured by the alkaline hematin method. The primary efficacy analysis is the treatment comparison between the relugolix Group A and the placebo Group B performed using a Cochran-Mantel-Haenszel (CMH) test statistic for proportions of	

responders stratified by the Parent study baseline mean menstrual blood loss (< 225 mL vs ≥ 225 mL), geographic regions (North America vs Other) and the duration of relugolix exposure at Week 52/Baseline (28 weeks vs 52 weeks).

The study will be considered positive if the treatment effect for the primary endpoint is statistically significant with 2-sided p-value < 0.05. The point estimate and 2-sided 95% confidence interval (CI) for treatment difference in responder rates for the primary efficacy endpoint will be calculated.

Efficacy data will be summarized on the modified Intent-to-Treat Population (mITT) defined as all randomized patients who took at least one dose of randomized study drug. The analyses methods for efficacy endpoints are similar to those used for the Parent studies, unless otherwise specified in the Statistical Analysis Plan (SAP).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, and bone mineral density determined by DXA. Safety data analyses will be performed on the Safety Population defined as all randomized patients who receive at least one dose of randomized or open-label study drug during the study.

Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the study Week52/Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 52/Baseline and Week 104/Early Termination visits. The absolute values, change, and percent change from the Parent study Baseline, and Z-scores will be summarized by visit and study treatment group. The mean percentage change from Week 52/Baseline to Week 104 in bone mineral density and corresponding 95% CI will be provided for each treatment group.

Pharmacodynamics

Pharmacodynamic estradiol concentration data (pre-dose concentration of estradiol at Week 56) will be listed and summarized by treatment arm and visit.

Sample Size Estimation

This Randomized Withdrawal study is an extension of the OLE study. The sample size of this study will be based on approximately the number of patients who have completed either Parent study (n = 780 patients in total), and who have participated in the OLE study (approximately n = 600 patients in total assuming ~ 20% dropout rate at 6 months from the Parent studies). Assuming the proportion of responders at Week 52 in the OLE study is about 60%, it is estimated that approximately 360 patients will be responders.

With 360 patients in the randomized cohort, the study will have at least 90% power to detect a difference of 20% or greater between relugolix Group A and placebo Group B for the primary endpoint. The following assumptions are used to determine the sample size for this study:

- 2-sided type I error rate: 0.05
- Randomization: 1:1
- Responder rate for placebo Group B: 40%
- Responder rate for relugolix Group A: 60%
- Dropout rate: 20%.

Stratification factors for Randomization

- Baseline MBL volume in the Parent study (< 225 mL vs ≥ 225 mL)
- Geographic region (North America vs Europe vs Latin America vs Rest of World)
- Duration of exposure to relugolix (28 weeks vs 52 weeks).

Stratification by the 4 geographic regions (North America vs Europe vs Latin America vs Rest of World) will be used for managing the supply of investigational product. For the purpose of stratified data analyses, the 4 regions will be pooled into 2 groups (North America vs Other) where Other includes Europe, Latin America and Rest of World.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-035

PERIOD	TREATMENT PERIOD													SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3001/3002)	**Week 52/Baseline (Week 52 of OLE Study; Baseline of Study)**	**Wk 52, Day 1**	**Wks 56, 60**	**Wk 64**	**Wks 68, 72**	**Wk 76**	**Wks 80, 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104 (or Early Termination of Study Drug) [a]**	**Unscheduled [b]**	**Follow-up (~30 days after last dose of study drug) [c]**
Visit Window (days)	OLE Study Day 365 + 10		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+ 10	-	- 3 to + 18
Informed Consent	X [d]													
Review Eligibility Criteria	X													
Concomitant Medications [e]	X [f]		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X [f]					X						X	X [g]	X
Weight	X [f]					X						X	X [g]	X
Complete Physical Exam	X [f]											X		
Gynecologic Exam	X											X		
Signs and Symptoms-Directed Physical Exam [h]			X	X	X	X	X	X	X	X	X		X [g]	X
12-Lead ECG [i]	X [f]												X [g]	
Clinical Laboratory Tests [j]	X [f]			X		X						X	X [g]	X
Urinalysis	X [f]					X						X	X [g]	
Pregnancy Test (Urine)	X [f]		X	X	X	X	X	X	X	X	X	X	X [g]	X
Estradiol levels	X		X [k]											
FSH [l]						X								

PERIOD	**TREATMENT PERIOD**													**SAFETY FOLLOW-UP**
VISIT NAME (Timing is relative to MVT-601-3001/3002)	**Week 52/Baseline (Week 52 of OLE Study; Baseline of Study)**	**Wk 52, Day 1**	**Wks 56, 60**	**Wk 64**	**Wks 68, 72**	**Wk 76**	**Wks 80, 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104 (or Early Termination of Study Drug) [a]**	**Unscheduled [b]**	**Follow-up (~30 days after last dose of study drug) [c]**
Visit Window (days)	OLE Study Day 365 + 10		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+ 10	-	- 3 to + 18
Transvaginal Ultrasound [m]	X [f]												X [g]	
Bone Densitometry [n]	X [f]											X [o p]	X [g]	
Dispense Treatment [q]	X		X	X	X	X	X	X	X	X	X	X	X [g]	
Take Study Drug Dose in Clinic [r]			X	X	X	X	X	X	X	X	X	X	X [g]	
Daily Self-Administration of Study Drugs		X [s]	X										X [g]	
Daily Completion of Paper Bleeding Diary [t]	X												X [g]	
Dispense Feminine Products	X		X	X	X	X	X	X	X	X	X	X	X [g]	
Feminine Product Collection and Venous Blood Sample [u]	X [f]		X	X	X	X	X	X	X	X	X	X	X [g]	
Treatment Compliance	X [f]		X	X	X	X	X	X	X	X	X	X	X [g]	
SF-36 Questionnaire	X		X	X	X	X	X	X	X	X	X	X		
PGA for function and symptoms Questionnaire	X		X	X	X	X	X	X	X	X	X	X		
WPAI-UF Questionnaire	X		X	X	X	X	X	X	X	X	X	X		
UFS-QoL Questionnaire	X			X		X		X			X	X		
Adverse Event Collection	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery														X

Abbreviations: BP, blood pressure; ECG, electrocardiogram; HR, heart rate; PGA, Patient Global Assessment; SF-36, Short Form (36) Health Questionnaire; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life; WPAI-UF, Work Productivity Activity Index-Uterine Fibroid

[a] The Week 104 visit should occur on or after the 2-year anniversary of Study Day 1 of the Parent study.
[b] Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.
[c] The Safety Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit.
[d] May be signed up to 30 days prior to the Week 52/Baseline visit or during the Week 52/Baseline visit. Enrollment in MVT-601-035 is defined by administration of the first dose of MVT-601-035 study drug.
[e] Record all prescription and nonprescription drug and supplements taken from the Week 52/Baseline visit through the Safety Follow-up period.
[f] This is an MVT-601-3003 (OLE study) Week 52 procedure that serves as the Week 52/Baseline procedure for MVT-601-035 and is covered under the informed consent for the OLE study.
[g] The indicated procedure may be performed at the unscheduled visit based on the purpose of the visit (e.g., follow-up for an adverse event or abnormal laboratory test).
[h] The exam may include a gynecologic examination, if indicated based on signs and symptoms.
[i] The 12-lead ECG will be submitted for central reading at the Week 52/Baseline visit. Any subsequent ECGs performed at investigator discretion will be read locally.
[j] Clinical laboratory tests required include clinical chemistries and a complete blood count. At the Week 52/Baseline visit and Week 104 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.
[k] Pre-dose specimen drawn at Week 56 only.
[l] Specimen for FSH will be collected and stored until the study is unblinded. The assay for FSH will be performed after unblinding on amenorrhoeic patients who were assigned to placebo.
[m] Transvaginal ultrasound, with or without transabdominal ultrasound, and with or without saline or gel contrast, is performed to determine uterine and myoma volumes and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size. Results must be submitted to a central reader.
[n] Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading.
[o] This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 60 or earlier. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.
[p] Patients with a bone mineral density loss of > 7% at their Week 104/Early Termination visit relative to Parent study Baseline measurement will undergo a follow-up bone densitometry scan at 6 (± 1) months and will be contacted to question them about medications and conditions (estradiol, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.
[q] Patients will be dispensed randomized treatment at the Week 52/Baseline visit, for self-administration beginning the following day, Week 52, Day 1. Randomized treatment will be dispensed at subsequent visits until HMB (MBL ≥ 80 mL) is documented by alkaline hematin testing. When HMB has been documented, the patient will be invited for a visit to begin retreatment with open-label study drug. The timing of that visit should be within 7 days of the onset of the patient's next menses (Cycle day 1-7 where Cycle day 1 is the first day of menstrual bleeding).
[r] Patients will take the first dose of study drugs for this study once daily starting at Week 52, Day 1 (self-administered with phone follow-up). The last dose of study drug will be taken in the clinic during the Week 104/Early Termination visit.
[s] Site to call patient and confirm first dose of study drug was taken that day.
[t] Patients enter diary information on menstruation status and feminine product use.
[u] Patients will collect and return all stained and soiled feminine products to the site with the initiation of randomized study drug treatment until return of heavy menstrual bleeding (MBL ≥ 80 mL) is observed. Collection will resume following the initiation of retreatment with open-label relugolix with add back and continue until MBL is observed to be < 80 mL on two consecutive collections. When the feminine products are returned, a venous blood sample (for hemoglobin) is to be collected and sent with the products to the central laboratory conducting the alkaline hematin assessment.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 75% of women by the onset of menopause. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment [Stewart, 2001; Stewart, 2017]. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy, and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids, and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size. However, they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, nonsteroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence of heavy menstrual bleeding after myomectomy is common, with at least 25% of women requiring additional treatment [Stewart, 2015; Marret, 2012; ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure with more than 200,000 hysterectomies performed annually in the United States (US) for uterine fibroids [Farquhar, 2002; Wu, 2007]. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel, or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection, and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the US suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012; Gliklich, 2011]. There is a great need for a safe and efficacious medicine that can decrease the symptoms of uterine fibroids so women have an alternative to myomectomy and hysterectomy.

2.2. Relugolix

The current relugolix Investigator's Brochure summarizes the nonclinical toxicology and previous human experience with relugolix. The previous human experience with relugolix includes results of phase 1 and phase 2 studies evaluating relugolix monotherapy in women with uterine fibroids or endometriosis and in men with prostate cancer, and phase 3 studies in women with uterine fibroids. The Investigator's Brochure also provides a full discussion of the safety profile of relugolix.

2.2.1. Indication

Relugolix 40 mg with estradiol 1.0 mg/norethindrone acetate 0.5 mg (relugolix with E2/NETA) is being developed as a once-daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily, and the proposed doses of estradiol and norethindrone acetate are 1.0 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly selective high-affinity small-molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes human GnRH receptors present on gonadotropin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor when treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives of this Randomized Withdrawal study are to evaluate the long-term efficacy and safety of relugolix with E2/NETA, once daily, for up to 104 weeks in patients with uterine fibroids who have completed a total of 52 weeks of treatment including 24-week treatment period in a Parent study (study MVT-601-3001 or study MVT-601-3002) and 28-week treatment period of the OLE study and who meet the definition of responder. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.

Primary and secondary assessment of efficacy and safety assessments will be made in the following two study treatment groups:

- Group A: 52 weeks of relugolix with E2/NETA, once daily;
- Group B: 52 weeks of placebo relugolix plus a capsule of placebo estradiol/norethindrone acetate.

Week 52 of the OLE study will define the baseline for this Randomized Withdrawal study and will be used as the reference point for all changes from baseline-related endpoints. The Week 48 blood loss volume establishes responder status. Menstrual blood loss volume in this study will be compared to the threshold of 80 mL.

Objective(s)	Endpoint(s)
<u>Primary Efficacy</u>	
• To evaluate the long-term effect of relugolix with E2/NETA, once daily, compared with placebo on menstrual blood loss at Week 76 (24 weeks after randomization).	• Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the Randomized treatment period) as measured by the alkaline hematin method.

Objective(s)	Endpoint(s)
Secondary Efficacy	
• To evaluate the long-term effect of relugolix with E2/NETA, once daily compared with placebo on menstrual blood loss at 52 weeks after randomization.	• Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 104 (52 weeks of the randomized treatment period) as measured by the alkaline hematin method; • Change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period); • Percentage change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period).
• To evaluate the effect of retreatment with relugolix with E2/NETA on menstrual blood loss in patients whose menstrual blood volume returned to ≥ 80 mL during the 52-week randomized period.	• Proportion of patients who responded (menstrual blood loss volume of < 80 mL) to retreatment during the retreatment period among placebo patients whose menstrual blood volume returns to ≥ 80 mL during the 52-week randomized treatment period.

• To evaluate the long-term effect of relugolix with E2/NETA at 52 weeks after randomization on the following:
  • Achievement of amenorrhea
  • Resumption of menses
  • Resumption of heavy menstrual bleeding (HMB)
  • Hemoglobin
  • Health-related Quality of Life as measured by the Short Form (36) Health (SF-36) questionnaire
  • Patient Global Assessment (PGA) for function and symptoms
  • Work and Productivity impact as measured by the Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF) questionnaire
  • Disease-specific quality of life as assessed by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) questionnaire
	The following secondary endpoints will be assessed at Week 76 and Week 104 during the randomized treatment period:
	• Proportion of women achieving or maintaining amenorrhea;
	• Proportion of women whose menses has resumed (among those who were amenorrhoeic at Week 52/Baseline);
	• Time to resumption of menses;
	• Proportion of women with menstrual blood volume ≥ 80 mL at any timepoint during the 52-week randomized treatment period;
	• Time to resumption of menstrual blood volume ≥ 80 mL;
	• Change from Week 52/Baseline in hemoglobin;
	• Change from Week 52/Baseline in SF-36 domain and summary component scores;
	• Change from Week 52/Baseline in PGA for function and symptoms score;
	• Change from Week 52/Baseline in the WPAI-UF scores;
	• Change from Week 52/Baseline in the UFS-QoL scale and sub-scale scores as well as the total score.

Objective(s)	Endpoint(s)
Pharmacodynamic	
• To characterize the pharmacodynamic (PD) effect of withdrawal from relugolix with E2/NETA	• Pre-dose concentration of estradiol at Week 56
Safety	

• To evaluate the safety and tolerability of relugolix with E2/NETA, once daily, for up to an additional 52 weeks, in patients who previously completed (responders and partial responders) the OLE study
  • Adverse events
  • Changes in bone mineral density
	• Incidence of adverse events, change in vital signs and clinical laboratory tests;
	• Percent change from Week 52/Baseline to Week 104 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This Randomized Withdrawal study (MVT-601-035) is an international phase 3 double-blind, placebo-controlled study that will enroll eligible patients with uterine fibroids who have completed the 24-week treatment period in a Parent study (study MVT-601-3001 or study MVT-601-3002) and the 28-week treatment period of the OLE study. When including treatment during the Parent study and the OLE study, patients completing this Randomized Withdrawal study will have received up to a total of 104 weeks of treatment with relugolix.

Study Population: All patients completing the OLE study with a response to treatment and consenting will be eligible to participate. Approximately 360 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.

Objectives: The objectives of the study are to evaluate long-term efficacy and safety of treatment with relugolix with E2/NETA for up to 104 weeks (total treatment duration includes the Parent study, OLE study, and Randomized Withdrawal study).

Approximately 360 patients completing the OLE study and meeting the definition of responder and all other eligibility criteria will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA, once daily or placebo for up to 52 weeks. For patients whose menstrual bleeding returns to ≥ 80 mL (heavy menstrual bleeding), treatment with open-label relugolix with E2/NETA will be restarted. A Schedule of Activities is provided in Table 1-1.

Screening and Baseline Procedures: Screening procedures will be done on the same day as the Week 52 visit for OLE. This visit will be referred to as the "Week 52/Baseline visit". The Week 52/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments,

transvaginal ultrasound, and endometrial biopsy (only if required). When Week 52/Baseline procedures in the OLE study have been completed, the investigator will assess patient eligibility for participation in this study. The eligibility assessment will be based on data available at the Week 52/Baseline visit. No study procedures will be performed until the consent form is signed. Patients will receive the last dose of study drug in the OLE study on the day of the Week 52/Baseline visit (per the OLE protocol) and will be dispensed study drug for this Randomized Withdrawal study in the clinic after the patient is determined to be eligible for this study and has provided informed consent to participate. The first dose of study drug for the Randomized Withdrawal study will be self-administered the next morning following the Week 52/Baseline visit. Dosing will be confirmed by telephone.

Post-baseline Procedures: All post-baseline procedures are provided in the Schedule of Activities (Table 1-1).

Patients will be asked to provide feminine products for alkaline hematin analysis at each visit until the analysis confirms the return of heavy menstrual bleeding (defined as menstrual blood loss of ≥ 80 mL). The patients will then be offered retreatment with open-label relugolix with E2/NETA (latter also referred to as "add-back" in context of hormonal "add-back") with the onset of the next menses. They will resume collection of feminine products for alkaline hematin analysis until two consecutive analyses confirm resolution of heavy menstrual bleeding (menstrual blood loss of < 80 mL). Patients who experience a return of heavy menstrual bleeding (or terminate early because they have a return of heavy menstrual bleeding) but decline retreatment with open-label study drug will complete an Early Termination visit and a 30-day Safety Follow-up visit.

At the Week 104/Early Termination visit, all other patients will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA). Patients will complete the bleeding diary daily including compliance with study drug, vaginal bleeding, and use of feminine products.

The pharmacodynamic effect of withdrawal from relugolix with E2/NETA will be characterized by measuring the pre-dose concentration of estradiol at Week 56.

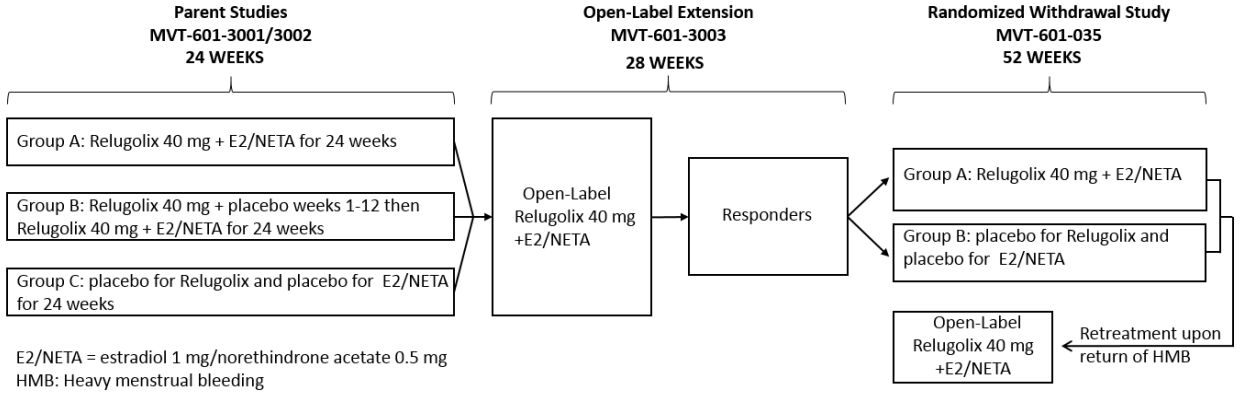
Safety will be assessed throughout the study by monitoring adverse events, vital signs and weight, physical examinations, clinical laboratory tests, and bone mineral density with DXA. Quality of life questionnaires will be completed according to the Schedule of Activities (Table 1-1).

Status of menstruation recovery will be documented at the Safety Follow-up visit (30 days after last dose of study drug). Patients whose menses have not resumed as of the Safety Follow-up visit and for whom there is no explanation for the lack of resumption (e.g., medical procedure or medications) will be contacted again by telephone 12 (± 2) weeks after the Safety Follow-up visit to determine if menses have resumed. These patients will be asked about factors that may affect the resumption of menses.

If a patient enrolls directly into another relugolix clinical study upon completion of the Week 104/Early Termination visit, then the Safety Follow-up visit and the follow-up procedures performed under this protocol may be waived.

A schematic of the MVT-601 Uterine Fibroid Program including the MVT-601-035 Study is provided in Figure 4-1.

Figure 4-1 MVT-601 Uterine Fibroid Program Schematic



4.2. Discussion of Study Design, Including Dosing

This Randomized Withdrawal study (MVT-601-035) is an extension of the 2 replicate, 24-week phase 3 Parent studies (MVT-601-3001 and MVT-601-3002) and subsequent 28-week open-label extension study (MVT-601-3003). The Parent studies and open-label extension study were designed to establish the efficacy and safety of relugolix with E2/NETA, once daily, for up to 52 weeks. This subsequent 52-week Randomized Withdrawal study provides additional efficacy and safety data for up to 104 weeks of treatment. The primary objective is to assess the long-term efficacy of relugolix with E2/NETA, once daily, for up to 104 weeks on reduction of heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. Because heavy menstrual bleeding due to uterine fibroids is a chronic condition in premenopausal women, this investigation is clinically relevant since patients are anticipated to require ongoing therapy.

In this design, the long-term efficacy of relugolix with E2/NETA will be assessed by comparing the maintenance of response in patients receiving continuous treatment to that in patients who are withdrawn from therapy. Patients who responded to open-label relugolix with E2/NETA in the OLE will be randomly assigned to continued active treatment or placebo in this study. Upon relapse, i.e., the return of heavy menstrual bleeding (MBL $\geq$ 80 mL), retreatment with open-label relugolix with E2/NETA, once daily, will be permitted. This design allows for placebo-controlled assessment of maintenance of efficacy while minimizing the duration of time in which symptomatic patients are without treatment. The effect of active treatment will be demonstrated by observing the difference in response between continued active treatment and placebo groups.

This design also affords the opportunity to assess the effectiveness of retreatment. This is important because, in clinical practice, interruption of treatment for variable lengths of time may occur due to circumstances such as poor compliance, desire to conceive, reimbursement issues, or intercurrent illness or surgery. Patients in this Randomized Withdrawal study who are given retreatment will be assessed to evaluate whether improvement in heavy menstrual bleeding can be recaptured.

The dose of relugolix for this Randomized Withdrawal study is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar

to those in the group of women treated with leuprolide subcutaneous injection (3.75 mg). Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the greatest reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development.

The 40 mg dose has been used in two phase 3 studies in Japan. One study demonstrated that relugolix 40 mg administered once daily to women experiencing heavy menstrual bleeding due to uterine fibroids reduced menstrual blood loss similar to leuprolide. The second study compared 40 mg relugolix to placebo in women having pain symptoms associated with uterine fibroids. The study included women with a Numerical Rating Scale (NRS) of score of ≥ 4 in the menstrual cycle prior to randomization. The proportion of subjects without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug was higher in the relugolix 40 mg group (48.5%) than in the placebo group (3.1%).

However, data on bone mineral density from DXA scanning in both the phase 2 and phase 3 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that limits dosing of relugolix to short term use only. To mitigate this known adverse consequence of estrogen suppression, relugolix is given with E2/NETA in phase 3 clinical studies, including this study. Estradiol 1.0 mg with norethindrone acetate 0.5 mg is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily led to less bone mineral density loss, these doses did not provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development. Additionally, based on the DXA data from the phase 2 study, these lower doses are not expected to prevent bone mineral density loss in a significant majority of women over 52 weeks of treatment.

The co-administration of hormonal add-back therapy with relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 104 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of supplemental estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2017]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in combination with relugolix in this Randomized Withdrawal phase 3 study is currently approved in the US as long-term hormone replacement

therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2017].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix with E2/NETA demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, a range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back hormonal therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2017]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this Randomized Withdrawal study (1.0 mg and 0.5 mg, respectively) are also used in the Parent studies (MVT-601-3001 and MVT-601-3002) and the OLE study (MVT-3003). This hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in well-designed phase 2 and phase 3 studies. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 double-blind, placebo-controlled Randomized Withdrawal study will assess long-term efficacy and safety of relugolix with E2/NETA, once daily, for the reduction of heavy menstrual bleeding associated with uterine fibroids, and for mitigation of bone mineral density loss and other side effects associated with a hypoestrogenic state such as hot flushes.

This Randomized Withdrawal study will provide information on long-term efficacy and safety data for an additional 52 weeks of treatment, providing approximately 2 years of efficacy and safety data from the women with uterine fibroids treated with relugolix in the Parent studies (MVT-601-3001 and MVT 601-3002) and the OLE (MVT 601-3003) study.

4.3. Selection of Study Population

The study population will include approximately 360 responders who have completed the 24-week treatment period in a Parent study (Study MVT-601-3001 or Study MVT-601-3002) and the 28-week treatment period of the OLE study with a response to treatment and meet all eligibility criteria for this study.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety.

Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for enrollment in this study only if all of the following inclusion criteria are met at the time of the Week 52/Baseline visit:

1. Completed the OLE study (MVT-601-3003);
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-035;

   Note: Procedures conducted as part of the OLE study that also serve as baseline procedures for this study may be done under the informed consent for the OLE study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including the Safety Follow-up period;
4. Is a responder: Has a menstrual blood loss of < 80 mL AND at least a 50% reduction from the Parent study baseline based on the results of the alkaline hematin testing performed on the feminine products returned at the Week 48 visit of the OLE. Results from Week 44 may be used if Week 48 data is unavailable;
5. Has a negative urine pregnancy test at the Week 52/Baseline visit;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the treatment period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 24 weeks prior to the Week 52/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 16 weeks prior to the Week 52/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (e.g., Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

4.3.2. Exclusion Criteria

None of the following criteria may be true for a patient to be eligible for enrollment into this study:

1. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-

guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the Parent study or OLE study;

2. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (e.g., bilateral hip replacement or spinal hardware in the lumbar spine);
3. Anticipates use of any prohibited medications as detailed in Section 5.9.1;
4. Has developed any contraindication to treatment with estradiol or norethindrone acetate, including:
   a. Known or suspected breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism;
   d. Active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. Porphyria;
5. Has current active liver disease from any cause;
6. Has a new diagnosis of a systemic autoimmune disease (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;
7. Had any of the following clinical laboratory abnormalities at the OLE study Week 48 visit or any subsequent visit:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
   c. Hemoglobin < 8 g/dL despite iron supplementation;
8. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 4 weeks after the last dose of study drug, or plans to donate ova during the study period or within 8 weeks after the last dose of study drug;
9. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor.
10. Met a withdrawal criterion in the OLE study.

4.4. Method of Assigning Patients to Treatment Group and Patient ID Number

Eligible patients who sign consent will be identified with the same Patient Identification Number assigned to the patient during the OLE study. All patients completing the OLE study with a

response to treatment and consenting will be eligible to screen. Once eligibility is confirmed, they will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA, once daily or placebo for up to 52 weeks.

4.5. Removal of Patients from Therapy

Completion of the Week 104 visit with appropriate safety follow-up defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 104 visit on the Schedule of Activities; Table 1-1) and will have a follow-up visit to assess safety approximately 30 days after the end of study drug treatment (i.e., after the patient's last dose of study drugs).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to an undue risk to the patient if dosing continued;
- If it is discovered after enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- If an iron deficiency anemia related to heavy menstrual bleeding develops with a hemoglobin < 8g/dL and is unresponsive to iron supplementation;
- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the Parent study Baseline at lumbar spine, total hip, or femoral neck based on the OLE study Week 52 DXA assessment of bone mineral density;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; or missing multiple study visits;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous noncompliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should make at least 3 documented attempts to contact the subject by telephone, or if necessary by certified letter so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.6. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded. Patients must agree to use nonhormonal contraception throughout the study unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 52/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™) at least 4 months prior to the Week 52/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Has a nonhormonal intrauterine device (e.g., Paragard®) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as described below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of contraception for whom none of the above methods apply are:

- Condom (male or female condom) with or without spermicide (cream, spray, foam, gel, suppository, or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm with signing of the consent form that they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 2 months following the last dose of study drug.

A patient may start hormonal contraception 4 weeks after her last study dose of study drug provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

Approximately 360 patients completing the OLE study and meeting the definition of responder and meeting all other eligibility criteria will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA (relugolix with add-back) or placebo for up to 52 weeks.

- Group A: 52 weeks of oral relugolix with E2/NETA, once daily;
- Group B: 52 weeks of placebo relugolix plus a capsule of placebo estradiol/norethindrone acetate.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, and color. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

After randomization, if the alkaline hematin analysis confirms the return of heavy menstrual bleeding (defined as menstrual blood loss of ≥ 80 mL) the patient will be offered retreatment at their next visit with open-label relugolix with add-back for the remainder of the treatment period.

Descriptions of all study drugs are provided in Table 5-1.

Table 5-1 Description of MVT-601-035 Study Drugs

Name of Investigational Product	Blinded and Open-Label Relugolix	Relugolix Placebo	Blinded Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo	Open-Label Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material	A Swedish orange capsule with placebo back-fill material	Round, white, biconvex, film-coated tablet
Dosage Form	Tablet	Tablet	Capsule	Capsule	Tablet
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / Norethindrone acetate 0.5 mg	0 mg	Estradiol 1.0 mg / Norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg)/norethindrone acetate (0.5 mg) is a fixed-dose combination product.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients.

The fixed-dose combination tablet of estradiol 1.0 mg/norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

5.3. Randomization and Stratification

Patients are randomized 1:1 ratio to blinded treatment with oral relugolix with E2/NETA (relugolix with add-back) or placebo. Stratification factors for randomization are as follows:

- Baseline MBL volume in the Parent study (< 225 mL vs ≥ 225 mL)
- Geographic region (North America vs Europe vs Latin America vs Rest of World)
- Duration of exposure to relugolix (28 weeks vs 52 weeks).

5.4. Directions for Administration

The study drugs should be taken in the fasted state (water, tea, or coffee are allowed) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study drugs should be taken as close as possible to the same time of morning each day.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated using adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Patients may subsequently be restarted on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20 – 25°C (68 – 77^{0}F) (with excursions permitted ± 5°C) to 15 - 30°C (59 - 86^{0}F) permitted until it is used or returned to the sponsor (or designee). Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, lot/batch number, expiry date, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

For randomized treatment, relugolix 40 mg will be supplied to the study site in blister cards. It will be co-packaged with the estradiol/norethindrone acetate. Open-label relugolix will be supplied in a bottle, and the open-label estradiol/norethindrone acetate will be supplied in a dial pack.

5.7. Blinding

During the double-blind Randomized Treatment and through the Safety Follow-up period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment and the decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator. However, the investigator should attempt to contact the medical monitor or appropriate study personnel to discuss options before unblinding the patient's treatment assignment unless the urgency of the medical situation precludes this. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

The sponsor (or designee) may unblind the treatment assignment for any patient with a serious adverse event.

For randomized patients whose menstrual blood volume returns to ≥ 80 mL during the 52-week randomized treatment period, therefore, will get retreatment with oral relugolix with E2/NETA, their randomized treatment assignment information is blinded during the 52-week randomized treatment period for all patients, investigators, and sponsor staff or representatives involved in the conduct of the study.

5.8. Study Drug Accountability and Treatment Compliance

Patients should bring all unused and used study drugs to each study visit. Study drug accountability will be conducted, and results will be recorded. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Prior and Concomitant Medications and Non-Drug Therapies

5.9.1. Prohibited Medications

Table 5-2 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 5-2 are prohibited at any time during the study through the to the Safety Follow-up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-2 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-Androgens	danazol	
Anti-convulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	All other anticonvulsants are allowed.
Aromatase Inhibitors	anastrozole letrozole	

Drug Class	Examples	Comments
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine Devices	Levonorgestrel intrauterine system	
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin clopedigril tranexamic acid vitamin k preparations factor Xa inhibitors	
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use (at screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study is prohibited. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration ($\leq$ 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.

Drug Class	Examples	Comments
P-glycoprotein Inducers	avasimibe carbamazepine phenytoin rifampin St. John's Wort tipranavir/ritonavir	For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol[g] clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelor verapamil	For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone

a. Roxithromycin is allowed
b. All other angiotensin converting enzyme inhibitors are allowed
c. Tacrolimus is allowed
d. Amlodipine and nifedipine are allowed
e. Fluconazole is allowed
f. Integrase inhibitors are allowed
g. Metoprolol and atenolol are permitted

5.9.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.9.2.1. Analgesics

From the Week 52/Baseline visit to the Week 104/Early Termination visit, the use of analgesics for uterine fibroid-associated pain should be in accordance with the local standard of care and at the discretion of the investigator.

5.9.2.2. Iron Therapy

Women who enter the Randomized Withdrawal study on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron-deficiency anemia during the study, defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.9.3. Prohibited Non-Drug Therapies

Surgical and other interventional treatment of uterine fibroids is prohibited from the Week 52/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1-1). Study procedures are briefly described in Section 6.5. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Table 1-1). The study is divided into 2 periods: Treatment period (Table 1-1) and Safety Follow-up period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Treatment Period (Week 52/Baseline to Week 104)

As denoted in the Schedule of Activities (see Table 1-1), certain Week 52 visit procedures in the OLE study will serve as the Week 52/Baseline procedures for patients who are interested in participating in this Randomized Withdrawal study, and these Week 52 procedures will be performed under the informed consent for the OLE study.

Patients will be required to sign an informed consent form for the Randomized Withdrawal study and will be eligible if they meet all the eligibility criteria.

Once eligibility is determined, all additional Week 52/Baseline visit procedures described in the Schedule of Activities (see Table 1-1) that were not performed as part of the Week 52 visit of the OLE study will be completed. These include the following:

- Informed consent;
- Record concomitant medications;
- Dispense study treatment;
- Dispense feminine products;
- Record adverse events, if any.

Patients will record vaginal bleeding and feminine product use in a paper diary each day. Safety monitoring including physical examination, pregnancy tests, and adverse event assessment will

occur at each visit. Additional safety assessments will be performed as described in the Schedule of Activities (see Table 1-1). Bone densitometry will occur at the Week 52/Baseline, and Week 104/Early Termination visits. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 52/Baseline visit.

Study drug compliance will be reviewed at each visit.

Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 52/Baseline and Week 104/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether the patient fasted for the chemistry and lipid testing.

Patients will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA, once daily, or placebo beginning on the day following the Week 52/Baseline visit and continuing through the Week 104 visit.

Patients will receive their last dose of study drug in the OLE study on the day of the Week 52/Baseline visit (as per the OLE study protocol), and the patient will be provided blinded study drug to begin dosing the following day. The first dose of study drug will be self-administered the next morning following the Week 52/Baseline visit. After the Week 52/Baseline visit, a phone call will occur on Week 52 Day 1 (+ 2 days) to document the time of self-administration of the first dose of study drugs and record any reported adverse events. On-treatment study visits will occur every 4 weeks for a total of 104 Weeks. With the initiation of randomized treatment, patients will collect all stained/soiled feminine products and at the study visits return their feminine products for alkaline hematin testing. A venous blood sample (for hemoglobin) must be collected each time feminine products are returned and sent to the central laboratory conducting the alkaline hematin assessment. If the patient is having cyclic bleeding, the site must document the start and stop dates of the patient's menses corresponding to the collected feminine products. The paper diary recording vaginal bleeding and feminine product use should be reviewed at each visit to assess compliance with feminine product collection.

When the alkaline hematin analysis indicates MBL ≥ 80 mL, the patient will be asked to return with onset of the next menses, no later than cycle day #7 (where cycle day #1 is the first day of menstrual bleeding), to begin retreatment with open-label relugolix with E2/NETA. The timing of this visit may necessitate an unscheduled visit. The final dose of randomized treatment should be self-administered by the patient the day prior to presenting for retreatment. The first dose of retreatment with open-label relugolix with E2/NETA will be administered at the clinic visit. Feminine products do not need to be collected with the episode of menstrual bleeding associated with the initiation of retreatment, but once the episode is complete, all stained/soiled feminine products must be collected and returned at subsequent visits for alkaline hematin analysis until MBL < 80 mL is observed for two consecutive collections.

6.3. Early Termination Visit and Safety Follow-up Visit

All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104; however, for patients whose last dose of study drug is during Week 56, bone densitometry does not need to be

performed. However, densitometry may be performed at the investigator's discretion as an aid to adverse event follow-up.

Patients who experience a return of heavy menstrual bleeding (or terminates early because they have a return of heavy menstrual bleeding) but decline retreatment with open-label study drug will complete an Early Termination visit and a 30-day Safety Follow-up visit.

Patients (including those who complete the Week 104 visit and those who withdraw early from this study) will have a follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for uterine fibroids, whichever occurs first. However, the Safety Follow-up visit may be waived for patients who enroll directly into another relugolix clinical study upon completion of the Week 104 visit.

The Safety Follow-up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (Table 1-1) for individual study visit procedures during the Safety Follow-up visit.

6.4. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, to initiate retreatment, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance, and dispensation, etc., may be conducted as clinically indicated. See the Schedule of Activities (Table 1-1) for tests that may be performed, as indicated by the reason for a visit, at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform transvaginal ultrasound endometrial biopsy, or DXA, unless urgently indicated.

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Bleeding Diary

All women enrolled in the study will be provided with a paper bleeding diary along with instructions for its use. Patients will complete the diary daily including compliance with study drug, vaginal bleeding, and use of feminine products.

6.5.1.2. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and all stained/soiled products will be collected at each visit starting with the initiation of randomized study drug treatment. Product collection will continue at each visit unless heavy menstrual bleeding (MBL ≥ 80 mL) is observed. Collection will resume following the initiation of retreatment with open-label relugolix with E2/NETA and continue until MBL is observed to be < 80 mL on two consecutive collections. If the patient is having cyclic bleeding, the site must document the start and stop dates of the patient's menses. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to with the products to the the laboratory for the alkaline hematin analysis. Details regarding materials, process, and requirements for the menstrual blood loss collection are provided in the Study Reference Manual.

6.5.1.3. Transvaginal and Transabdominal Ultrasound

Transvaginal ultrasound will be performed for all subjects at the Week 52/Baseline visit as a part of the OLE study (MVT-601-3003). Once the transvaginal ultrasound is complete, a transabdominal ultrasound (with or without saline or gel contrast) may also be performed if the uterus cannot be adequately imaged on transvaginal ultrasound (e.g., due to enlarged size). Transvaginal ultrasound, with or without transabdominal ultrasound, is performed to determine uterine and myoma volumes. A single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device, as far as possible, to avoid inter-observer and inter-device variations. This single operator should be the same person, if possible, as previously assigned to the patient during her participation in the Parent study.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = $D1 \times D2 \times D3 \times \pi / 6$
Where:

- D1 = the longest diameter of the myoma or uterus (unit of length: cm)
- D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
- D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. Any ultrasounds performed after the Week 52/Baseline visit must be read locally.

6.5.1.4. Health Survey Standard (SF-36)

The Health Survey Standard (SF-36) is a validated 36-item questionnaire which measures quality of life across eight health domains that can be combined into a physical and a mental summary component score. (see Appendix 1). The SF-36 has a 4-week recall period and will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). With the exception of the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.1.5. Patient Global Assessment (PGA) for Function and Symptoms

The PGAs for Function and Symptoms are completed by the patient; they are based on a 5-point Likert scales and have a 4-week recall period (see Appendix 2). The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). Except for the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.1.6. Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF)

The Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF) is a validated instrument used to measure impairments in work and activities, which has been adapted for uterine fibroids (see Appendix 3). The WPAI-UF will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). Except for the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.1.7. Uterine Fibroid Symptom and Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QoL) is a validated instrument used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). The UFS-QoL will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). Except for the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

Patients should have weight measured while wearing indoor clothing and with shoes removed.

6.5.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.5.2.3. Physical and Gynecologic Exams

A complete physical examination will include examinations of head, ears, eyes, nose, mouth, thyroid, skin, heart and lung, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from previous assessments. The gynecologic examination will include breast and pelvic exams.

6.5.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities (see Table 1-1). Laboratory requisition forms must be completed, and samples must be clearly labeled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all laboratory tests will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

<table>
<tr><th>Chemistry</th><th>Hematology</th><th>Urinalysis</th></tr>
<tr><td rowspan="3">Potassium
Chloride
Bicarbonate
Blood Urea Nitrogen
Creatinine
Glucose
Calcium
Phosphate
Magnesium
Sodium
Albumin
Hemoglobin A1c
Creatine Kinase
Bilirubin Total
Alanine Aminotransferase
Aspartate Aminotransferase
Gamma-Glutamyl Transferase
Alkaline phosphatase</td><td>White Blood Cell (WBC) Count
WBC Differential
Red Blood Cell Count
Hemoglobin
Hematocrit
Mean Corpuscular Volume
Platelet Count
Red Blood Cell (RBC) morphology</td><td>Protein
Glucose
Blood
Urobilinogen
Bilirubin
Color and Clarity
pH
Leucocyte Esterase

Ketones
Nitrite
Specific Gravity
Urine Microscopy (reflex testing based on abnormal urine analysis)</td></tr>
<tr><th>Lipids</th><th>Pregnancy</th></tr>
<tr><td>Total Cholesterol
Low Density Lipoprotein
High Density Lipoprotein
Triglycerides</td><td>Pregnancy test (human chorionic gonadotropin)</td></tr>
<tr><th>Hormones</th><td colspan="2" rowspan="2"></td></tr>
<tr><td>Estradiol
FSH</td></tr>
</table>

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

To maintain blinding, concentrations of estradiol hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding. Specimens for FSH will be collected and stored until the study is unblinded. The assay for FSH will be performed after unblinding on amenorrhoeic patients who were assigned to placebo.

6.5.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at Week 52/Baseline visit in this study, as well as if needed to evaluate any signs or symptom that require an ECG to assess. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant. Any ECGs performed after the Week 52/Baseline visit will be read locally.

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3, and L4), total hip, and femoral neck (same leg within each patient). Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will be used at each site and operated in the same scan mode for all scans for each patient. This should be the same as used for the patient during the OLE study. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual subjects will be monitored by a central radiology laboratory over the course of the study.

Patients who experience a bone mineral density loss of ≥ 7% from the Parent study baseline at any of the anatomical sites assessed will be discontinued from the study and will undergo another bone densitometry scan as described below. Patients should be assessed for secondary

causes of bone loss and followed-up further if not improving on 6 months follow-up scan unless an alternative etiology has been identified.

Patients with a bone mineral density loss of ≥ 7% at lumbar spine, total hip, or femoral neck at their Week 104/Early Termination visit relative to Parent study baseline measurement will undergo another bone densitometry scan at 6 (± 1) months and will be contacted to obtain information about medications and conditions (e.g., pregnancy) that might affect bone mineral density through the time of the follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.

6.5.2.7. Status of Menstruation Recovery

If the first menstruation after the end of study treatment administration is observed before the Safety Follow-up visit, the date of onset of the first menstruation is recorded in the electronic case report form (eCRF). Patients whose menses has not resumed as of the Safety Follow-up visit for whom there is no explanation for the lack of resumption (e.g., medical procedure or medications) will be contacted again by telephone 3 (± 0.5) months after the Safety Follow-up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), clinical laboratory tests, ECGs, and bone mineral density assessments.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event include:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical

events (e.g., for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and

- An investigational abnormality (e.g., laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that do not meet the definition of an adverse event include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (e.g., planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent);
- Events of heavy menstrual bleeding, as heavy menstrual bleeding is quantified as an efficacy endpoint, unless meets seriousness criteria.

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted; however, study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been admitted to a hospital, independent of the duration of that hospitalization. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any

other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from the Week 52/Baseline visit is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events that jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local institutional review board (IRB) or institutional ethics committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

The patient's answers to study questionnaires will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Safety Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Table 1-1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life-threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the open-label Treatment period or Safety Follow-up period should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet serious adverse event criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 5.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or Week 52/Baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug-induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (i.e., potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein Barr virus);
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   - Alcoholic hepatitis;
   - Nonalcoholic steatohepatitis;
   - Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

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 contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the serious adverse event report form and is as follows:

Send completed Safety Report Forms to IQVIA RDS Inc:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All study sites	PPD	PPD

For questions on Serious Adverse Event/Adverse Event of Clinical Interest reporting, please call:

- North/South America: PPD
- Europe, Asia, Pacific, and South Africa: see region-specific phone numbers accompanying the Safety Report Form

The initial report should include:

- Study number (MVT-601-035);
- Site address and number;
- Investigator name;
- Patient Identification Number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity);
- Causal relationship to the study drug.

If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (i.e., more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for pharmacokinetic analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

Pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the pregnancy report forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc., should be included in pregnancy report form, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, weight, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, arthralgia, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine

fibroids. Hormonal add-back therapy with estradiol/norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (corrected QT interval [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD), reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator's Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of estradiol/norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the Parent studies.	Bone mineral density will be monitored at the Week 52/Baseline and Week 104/Early Termination visits with specified discontinuation and follow-up criteria, and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the Parent studies.	12-lead ECG at the Week 52/Baseline and Week 104/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzyme increases Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN.	Abnormal liver test results (AST or ALT > 3 x ULN) that develop during the Treatment period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the Parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable nonhormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.
Risk of Estradiol 1.0 mg/Norethindrone Acetate 0.5 mg Estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignancies, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the Parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 52/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (e.g., patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A Statistical Analysis Plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patient's study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% testing across primary and key secondary endpoints will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

The final analysis of efficacy and safety data will occur after approximately 360 patients (projected to be responders from the open-label extension study MVT-601-3003) who have been randomized and have had the opportunity to complete Week 104 visit or through the 30-day Safety Follow-up visit.

9.1. Randomization Methods

This is an international phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal study that will enroll eligible patients with uterine fibroids who have completed the 24-week treatment period in a Parent study (Study MVT-601-3001 or Study MVT-601-3002) and the 28-week treatment period of the OLE study. Patients completing the OLE study and meeting the definition of responder will be randomized 1:1 into two different treatment groups:

- Group A: 52 weeks of oral relugolix with E2/NETA, once daily;
- Group B: 52 weeks of placebo relugolix plus a capsule of placebo estradiol/norethindrone acetate.

Randomization will be stratified by the following factors:

- Geographic Region: North America vs Europe vs Latin America vs Rest of World;
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL; and
- Duration of relugolix exposure prior to randomization (28 weeks vs 52 weeks).

The four stratification levels (North America vs Europe vs Latin America vs Rest of World) for geographic region considered for randomization take drug supply monitoring into consideration. For the purpose of stratified data analyses, the 4 regions will be pooled into two groups (North American vs Other) where Other includes Europe, Latin America and Rest of World.

Statistical analyses for efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The modified Intent-to-Treat (mITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. The mITT Population will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the mITT Population who have no relevant major protocol violations, defined as a subset of all major protocol violations (details will be provided in the Statistical Analysis Plan). The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the mITT Population.

This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the mITT Population according to the randomized treatment assignment, and stratified analyses will be stratified by the randomization stratification factors. If the group of patients from any of the individual randomization stratification factors comprises less than 10% of the entire mITT population, this stratification factor will be ignored for stratified analyses.

9.3.1. Primary Efficacy Endpoint

The primary endpoint of the study is the proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the randomized treatment period) as measured by the alkaline hematin method. The primary endpoint of responder rate will be evaluated using the mITT Population.

Week 52 of the OLE study will define as the baseline for this Randomized Withdrawal study and will be used as the reference point for all changes from baseline-related endpoints. Although responder status is based on Week 48 of the OLE study, the menstrual blood loss (MBL) volume at the Week 52 period of the OLE study will establish the patient's baseline for evaluation of menstrual blood loss during the 52-week randomized treatment period of the study.

9.3.1.1. Primary Analysis

The primary hypothesis for the primary efficacy endpoint to be tested in this study is relugolix (Group A) is superior to placebo (Group B) with respect to the proportion of responders at Week 76 (24 weeks after randomization) based on the MBL volume analyzed by alkaline hematin method:

Null hypothesis H_{01}: $\pi^R \leq \pi^P$ vs Alternative hypothesis H_{a1}: $\pi^R > \pi^P$

where π^R and π^P are the responder rates for relugolix and placebo groups, respectively.

The primary efficacy analysis is the treatment comparison between the relugolix Group A and the placebo Group B performed using a Cochran-Mantel-Haenszel (CMH) test statistic for proportions of responders stratified by baseline mean menstrual blood loss in the Parent study (< 225 mL vs ≥ 225 mL), geographic region (North America vs Other) and the duration of relugolix exposure prior to randomization (28 weeks vs 52 weeks).

The study will be considered positive if the treatment effect for primary endpoint is statistically significant with 2-sided p-value < 0.05. The point estimate and 2-sided 95% confidence interval (CI) for treatment difference in responder rates for the primary efficacy endpoint will be calculated.

9.3.1.2. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint comparing Group A versus Group B will be performed to determine whether treatment effect is consistent across clinically meaningful subgroups. The difference in responder rates and their 95% confidence intervals will be displayed in a forest plot. Subgroups will include but not be limited to the following: baseline MBL volume in the Parent study (< 225 mL vs ≥ 225 mL), geographic region (North America vs Other), duration of exposure to relugolix prior to randomization (28 weeks vs 52 weeks) as well as other baseline subgroups such as age, and race. Details are provided in the Statistical Analysis Plan.

9.3.1.3. Sample Size Estimation

Because this is an extension of the OLE study, the sample size of this study will be based on approximately the number of patients who have completed a Parent study (n = 780 patients in total), and who participated in the OLE study (n = 600 patients in total assuming about 20% dropout rate at 6 months from the Parent studies). Assuming the proportion of responders at Week 52 in the OLE study is 60%, it is estimated that approximately 360 patients will be randomized into this study.

With 360 patients, the study will have at least 90% power to detect a difference of 20% or greater between relugolix Group A and placebo Group B for the primary endpoint. The following assumptions are used to determine the sample size for this study:

- 2-sided type I error rate: 0.05
- Randomization: 1:1
- Responder rate for placebo Group B: 40%
- Responder rate for Group A: 60%
- Dropout rate: 20%

9.3.2. Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed during the randomized treatment period or retreatment period:

- Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 104 (52 weeks of the randomized treatment period) as measured by the alkaline hematin method;
- Change from Week 52/Baseline to Week 76/Week 104 in menstrual blood volume (during the randomized treatment period);
- Percentage change from Week 52/Baseline to Week 76 / Week 104 (during the randomized treatment period);
- Proportion of patients who responded (menstrual blood loss volume of < 80 mL) to retreatment with relugolix 40 mg and E2/NETA during the retreatment period among placebo patients whose menstrual blood volume had returned to ≥ 80 mL during the 52-week randomized treatment period;

The following secondary endpoints will be assessed at Week 76 and at Week 104 during the randomized treatment period:

- Proportion of women achieving or maintaining amenorrhea;
- Proportion of women whose menses has resumed (among those who were amenorrhoeic at Week 52/Baseline);
- Time to resumption of menses;
- Proportion of women with menstrual blood volume ≥ 80 mL at any time point during the 52-week randomized treatment period;
- Time to resumption of menstrual blood volume ≥ 80 mL;
- Change from Week 52/Baseline in hemoglobin;
- Change from Week 52/Baseline in SF-36 domain and summary component scores;
- Change from Week 52/Baseline in PGA for function and symptoms scores;
- Change from Week 52/Baseline in the WPAI-UF scores;
- Change from Week 52/Baseline in the UFS-QoL Symptom Severity scale and subscales as well as total scores.

9.3.2.1. Secondary Efficacy Endpoint Analyses

During Randomized Treatment Period

For endpoints evaluating the change from Baseline, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, randomization stratification factors, and treatment by visit interaction included as fixed effects and Week 52/Baseline value included as a covariate. The dependent variable (change from Baseline) for each patient at each visit will be calculated based on visit windows specified in the final Statistical Analysis Plan. In addition, descriptive statistics will be provided by treatment group and by visit.

Change from baseline endpoints will be analyzed censoring the values at the time of retreatment with relugolix with E2/NETA. Details will be specified in the SAP.

For endpoints evaluating proportions, treatment comparisons will be performed using a stratified Cochran-Mantel-Haenszel test as appropriate.

Baseline menstrual blood loss is defined as total menstrual blood loss obtained from the Week 52/Baseline visit prior to the date of the first dose of study drug in this Randomized Withdrawal study as assessed by the alkaline hematin method. The menstrual blood loss during the last on-treatment cycle (Week 104) is the total menstrual blood loss during the last month (up to the last 35 days) on-treatment as assessed by the alkaline hematin method.

For time-to-event endpoints (time to achieving or maintaining a menstrual blood loss volume of < 80 mL 24 weeks after randomization, time to resuming menses, time to resumption of menstrual blood volume ≥ 80 mL), time-to-event will be defined as weeks from randomization of the Randomized Withdrawal study to first occurrence of the event. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions for each study treatment arm.

For binary endpoints, the point estimate and 2-sided 95% CI for the proportion will be provided by study treatment group.

During Retreatment Period

For placebo patients whose menstrual blood volume had returned to ≥ 80 mL during the 52-week randomized treatment period and received retreatment:

- the proportion of patients who responded to the retreatment (MBL < 80mL) will be estimated along with corresponding 95% CIs at the end of retreatment period
- mean change and mean % change in menstrual blood volume from retreatment to end of retreatment period.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Pharmacodynamic Analyses

Pharmacodynamic estradiol concentration data will be listed and summarized by treatment arm and visit.

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECGs, and results of measurements of bone mineral density by DXA.

The treatment-emergent period will be defined as the period of time from the first dose date of extension study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. 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 study Baseline versus post-baseline results. All data will be listed and summarized by visit. The change from study Baseline to each post-baseline study visit will be presented by study treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from study Baseline to each post-baseline study visit will be presented by study treatment group for each parameter.

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses.

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by the study treatment arm.

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

All BMD data will be listed and summarized by visit. The change, percent change from study Week 52/Baseline to Weeks 76 and 104 and associated 95% CIs will be presented by the study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 3%, 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the study treatment group.

Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a US investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This

requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for 1 year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient.

10.1.4. Confidentiality

The investigator must assure that patient's anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the Investigator's Brochure, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (e.g., history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;
   - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
   - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
   - Concomitant medication (including start and end date); and
   - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator's Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and

signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on Form FDA 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (i.e., pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 90 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 120 days in order to obtain patent protection if deemed necessary.

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APPENDICES

Appendix 1. Health Survey Standard (SF-36v2®)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your norma work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 2. Patient Global Assessment (PGA) for Function and Symptoms

Patient Global Assessment (for function)

How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. No limitation at all
2. Mild limitation
3. Moderate limitation
4. Quite a bit of limitation
5. Extreme limitation

Patient Global Assessment (for symptoms)

How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. Not severe
2. Mildly severe
3. Moderately severe
4. Very severe
5. Extremely severe

Appendix 3. Work Productivity Activity Impairment -Uterine Fibroids (WPAI-UF)

Work Productivity and Activity Impairment Questionnaire:
Uterine Fibroids V2.0 (WPAI:UF)

The following questions ask about the effect of uterine fibroid symptoms on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO _____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your uterine fibroid symptoms? *Include hours you missed on sick days, times you went in late, left early, etc., because of your uterine fibroid symptoms. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS *(If "0", skip to question 6.)*

English for USA – WPAI:UF V2.0 – 10/FEB/2016

5. During the past seven days, how much did your uterine fibroid symptoms affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If uterine fibroid symptoms affected your work only a little, choose a low number. Choose a high number if uterine fibroid symptoms affected your work a great deal.

Consider only how much uterine fibroid symptoms affected productivity while you were working.

Uterine fibroid symptoms had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Uterine fibroid symptoms completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your uterine fibroid symptoms affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If uterine fibroid symptoms affected your activities only a little, choose a low number. Choose a high number if uterine fibroid symptoms affected your activities a great deal.

Consider only how much uterine fibroid symptoms affected your ability to do your regular daily activities, other than work at a job.

Uterine fibroid symptoms had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Uterine fibroid symptoms completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-65.

English for USA – WPAI:UF V2.0 – 10/FEB/2016

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

Pt. Initials: _____ **Pt. ID:** _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐	☐	☐	☐	☐
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐	☐	☐ 3	☐	☐
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐	☐	☐	☐	☐
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about traveling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling underclothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Appendix 5. Assessment of Abnormal Liver Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with estradiol/norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (e.g., right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (e.g., travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

CLINICAL STUDY PROTOCOL

Study Title:	An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix Co-administered with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-035
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 CH-4051 Basel Switzerland
Regulatory Identifier(s):	Eudra CT # 2018-001368-43 IND # 131161
Version and Effective Date:	Original: 11-July-2018 Amendment 1: 13-August-2018

SPONSOR SIGNATURE PAGE

An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix Co-administered with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Protocol Number: MVT-601-035

This protocol has been approved by Myovant Sciences GmbH. The following signatures document this approval.

PPD

PPD PPD

13. Aug. 2018
Date

PPD

PPD

PPD PPD

13-Aug-2018
Date

PPD

PPD

PPD PPD

13-Aug-2018
Date

PPD

PPD PPD

13 aug 2018
Date

INVESTIGATOR STATEMENT

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study understand their obligations and will comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate training and information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMD	Body Mass Data
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dihyroepiandrosterone
DXA	dual-energy x-ray absorptiometry
E2/NETA	estradiol 1.0 mg/norethindrone acetate 0.5 mg
ECG	electrocardiogram
eCRF	electronic case report form
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HMB	heavy menstrual bleeding
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MBL	menstrual blood loss
mITT	modified Intent-to-Treat
OLE	Open-label extension; LIBERTY EXTENSION; MVT-601-3003
PD	pharmacodynamic
PGA	Patient Global Assessment
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT Interval Corrected by the Fridericia Correction Formula
RBC	red blood cell
SF-36	Short Form (36)
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
WPAI-UF	Work Productivity Activity Impairment-Uterine Fibroids
ULN	Upper limit of normal
US	United States
WBC	white blood cells
WPAI-UF	Work Productivity Activity Impairment-Uterine Fibroids

1. PROTOCOL SYNOPSIS

Study Title	An International Phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal Study of Relugolix with Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-035
Location	Multinational, including North and South America, Europe, and South Africa
Study Centers	Approximately 240 sites
Study Phase	Phase 3
Target Population	Women 18 to 51 years old diagnosed with uterine fibroids who complete the open-label extension study MVT-601-3003 (OLE study) and who meet the definition of responder. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.
Number of Patients Planned	Approximately 360

Study Objectives	In women with uterine fibroids who complete the OLE study and are identified as responders, the efficacy objectives are as follows:
	<u>Primary Efficacy Objective</u>
	• To evaluate the long-term effect of relugolix 40 mg with estradiol 1.0 mg and norethindrone acetate 0.5 mg (relugolix with E2/NETA) once daily, compared with placebo on menstrual blood loss at Week 76 (24 weeks after randomization).
	<u>Secondary Efficacy Objectives</u>
	• To evaluate the long-term effect of relugolix with E2/NETA once daily, compared with placebo on menstrual blood loss at 52-weeks after randomization.
	• To evaluate the effect of retreatment with relugolix with E2/NETA on menstrual blood loss in patients whose menstrual blood volume returned to ≥ 80 mL during the 52-week randomized period.
	• To evaluate the long-term effect of relugolix with E2/NETA at 52 weeks after randomization on the following:
	  • Achievement of amenorrhea
	  • Resumption of menses
	  • Resumption of heavy menstrual bleeding (HMB)
	  • Hemoglobin
	  • Health-related quality of life as measured by the Short Form (36) (SF-36)
	  • Patient Global Assessment (PGA) for function and symptoms
	  • Work and productivity impact as measured by the Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF)

	• Disease-specific quality of life as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL). Pharmacodynamic Objectives • To characterize the pharmacodynamic (PD) effect of withdrawal from relugolix with E2/NETA. Safety Objectives • To evaluate the safety and tolerability of relugolix with E2/NETA once daily for up to an additional 52 weeks, in patients who previously completed (responders and partial responders) the OLE study. • Adverse events • Changes in bone mineral density.

Study Design

Overall Study Design: This is an international phase 3 double-blind, placebo-controlled, Randomized Withdrawal study that will enroll eligible patients with uterine fibroids who have completed the 24-week treatment period in a Parent study (study MVT-601-3001 or study MVT-601-3002) and the 28-week treatment period of the OLE (MVT-601-3003) study. When including treatment during the Parent study and the OLE study, patients completing this Randomized Withdrawal study will have received up to a total of 104 weeks of treatment.

Study Population: All patients who complete the OLE study with a response to treatment, provide informed consent, and met all eligibility criteria for study MVT-601-035 will be eligible to participate. Approximately 360 women (responders) with heavy menstrual bleeding associated with uterine fibroids will be enrolled. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.

Objectives: The objectives of the study are to evaluate long-term efficacy and safety of treatment with relugolix with E2/NETA for up to 104 weeks (total treatment duration includes the Parent study, OLE study, and Randomized Withdrawal study).

Treatment Assignment

Approximately 360 patients completing the OLE study and meeting the definition of responder and meeting all other eligibility criteria will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA or placebo, once daily, for up to 52 weeks. Stratification variables will include geographic region (North America vs Europe vs Latin America vs Rest of World), duration of relugolix exposure prior to randomization (28 weeks vs 52 weeks), and baseline menstrual blood loss volume in the Parent study (< 225 mL vs ≥ 225 mL). For patients whose menstrual bleeding returns to ≥ 80 mL (heavy menstrual bleeding), treatment with open-label relugolix with E2/NETA (latter also referred to as "add-back" in context of hormonal "add-back") will be restarted. A Schedule of Activities is provided in Table 1-1.

Screening and Baseline Procedures: The study consists of a screening period and a treatment period (randomized or open-label) of up to 52 weeks. Screening and baseline procedures will be done at the same visit for this Randomized Withdrawal study (referred to as the "Week 52/Baseline visit" in this study), which coincides with the Week 52 visit of the OLE study and will be defined as the date of completion of the last procedure in the OLE study (see Schedule of Activities; Table 1-1). The Week 52/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, transvaginal ultrasound, and endometrial biopsy (only if required). When Week 52/Baseline procedures in the OLE study have been completed, the investigator will assess patient eligibility for participation in this study. The eligibility assessment will be based on data available at the Week 52/Baseline visit. No study

procedures will be performed until the consent form is signed. Patients will receive their last dose of study drug in the OLE study on the day of the Week 52/Baseline visit (as per the OLE study protocol). Following confirmation that the patient is eligible for this Randomized Withdrawal study and has provided informed consent to participate, the patient will be provided blinded study drug to begin dosing the following day. The first dose of study drug will be self-administered the next morning following the Week 52/Baseline visit.

Post-baseline Procedures: Study participants will be randomized to take either blinded study treatment (relugolix with E2/NETA or placebo) orally once daily or, when retreatment is indicated, open-label relugolix with E2/NETA for up to additional 52 weeks (beyond the 52 weeks of previous treatment during the Parent/OLE studies). All post-baseline procedures are provided in the Schedule of Activities (Table 1-1). Patients will be contacted on Week 52/Day 1 to confirm initiation of self-administered dosing.

Patients will be asked to provide feminine products for alkaline hematin analysis at each visit. If the analysis confirms return of heavy menstrual bleeding (defined as menstrual blood loss of ≥ 80 mL) the patient will be offered retreatment with open-label relugolix with E2/NETA with the onset of the next menses. They will resume collection of feminine products for alkaline hematin analysis until two consecutive analyses confirm resolution of heavy menstrual bleeding (menstrual blood loss of < 80 mL). Patients will complete the bleeding diary daily including compliance with study drug, vaginal bleeding, and use of feminine products.

Safety will be assessed throughout the study by monitoring adverse events, vital signs and weight, physical examinations, clinical laboratory tests, and bone mineral density with dual-energy x-ray absorptiometry (DXA). Quality of life questionnaires will be completed according to the Schedule of Activities (Table 1-1). There is a Safety Follow-up visit (approximately 30 days after last dose of study drug) for all patients, and additional unscheduled follow-up visit(s) may be arranged at any time during the study for patients with study-related safety concerns, as needed.

The PD effect of withdrawal from relugolix with E2/NETA will be characterized by measuring the pre-dose concentration of estradiol at Week 56.

Status of menstruation recovery will be documented at the Safety Follow-up visit (30 days after last dose of study drug). Patients whose menses have not resumed as of the Safety Follow-up visit and for whom there is no explanation for the lack of resumption (e.g., medical procedure or medications) will be contacted again by telephone 12 (± 2) weeks after the Safety Follow-up visit to determine if menses have resumed. These patients will be asked about factors that may affect resumption of menses.

If a patient enrolls directly into another relugolix clinical study upon completion of the Week 104/Early Termination visit, then the Safety Follow-up visit, and the follow-up procedures performed under this protocol may be waived.

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria are met at the time of the Week 52/Baseline visit:

1. Completed the OLE study;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-035;

   Note: Procedures conducted as part of the OLE study that also serve as baseline procedures for this study may be done under the informed consent for the OLE study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including the Safety Follow-up period;

4. Is a responder: Has a menstrual blood loss of < 80 mL AND at least a 50% reduction from the Parent study baseline based on the results of the alkaline hematin testing performed on the feminine products returned at the Week 48 visit of the OLE study. Results from Week 44 may be used if Week 48 data is unavailable;
5. Has a negative urine pregnancy test at the Week 52/Baseline visit;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the treatment period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 24 weeks prior to the Week 52/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 16 weeks prior to the Week 52/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (e.g., Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study:

1. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the Parent study or OLE study;
2. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (e.g., bilateral hip replacement or spinal hardware in the lumbar spine);
3. Anticipates use of any prohibited medications as detailed in Section 5.9.1;
4. Has developed any contraindication to treatment with estradiol or norethindrone acetate including:
   a. Known or suspected breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism;
   d. Active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. Porphyria;
5. Has current active liver disease from any cause;
6. Has a new diagnosis of a systemic autoimmune disease (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic

arthritis, vasculitic syndromes, etc.). Psoriasis not requiring or anticipated to require systemic therapy is permitted; 7. Had any of the following clinical laboratory abnormalities at the OLE study Week 48 visit or any subsequent visit: a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome); c. Hemoglobin < 8 g/dL despite iron supplementation; 8. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 4 weeks after the last dose of study drug, or plans to donate ova during the study period or within 8 weeks after the last dose of study drug; 9. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor; 10. Met a withdrawal criterion in the OLE study.	
Dose and Route of Administration	Test Product Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The hormonal add-back therapy will be over-encapsulated. Reference Product Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active hormonal add-back therapy in size, shape, and color. Open-label Product Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. Study treatment will be self-administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 52 weeks.
Criteria for Evaluation	Inferential efficacy assessments will be made on data observed from Week 52 to Week 104 between the following two study treatment groups: • Group A: 52 weeks of oral relugolix with E2/NETA, once daily; • Group B: 52 weeks of placebo relugolix plus capsule of placebo estradiol/norethindrone acetate. Week 52 of the OLE study will define the Baseline for this Randomized Withdrawal study and will be used as the reference point for all changes from baseline-related endpoints. The menstrual blood loss (MBL) volume at the Week 52 period of the OLE study will establish the patient's baseline for evaluation of menstrual blood loss during the 52-week randomized treatment period of this Randomized Withdrawal study.

	Primary Efficacy Endpoint • Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the randomized treatment period) as measured by the alkaline hematin method. Secondary Efficacy Endpoints • Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 104 (Week 52 of the randomized treatment period) as measured by the alkaline hematin method; • Change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period); • Percentage change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period); • Proportion of patients who responded (menstrual blood loss volume of < 80 mL) to retreatment with relugolix with E2/NETA during the retreatment period among placebo patients whose menstrual blood volume had returned to ≥ 80 mL during the 52-week randomized treatment period. The following secondary endpoints will be assessed at Week 76 and at Week 104 during the randomized treatment period: • Proportion of women achieving or maintaining amenorrhea; • Proportion of women whose menses has resumed (among those who were amenorrhoeic at Week 52/Baseline); • Time to resumption of menses; • Proportion of women with menstrual blood volume ≥ 80 mL at any timepoint during the 52-week randomized treatment period; • Time to resumption of menstrual blood volume ≥ 80 mL; • Change from Week 52/Baseline in hemoglobin; • Change from Week 52/Baseline in SF-36 domain and summary component scores; • Change from Week 52/Baseline in PGA for function and symptoms score; • Change from Week 52/Baseline in the WPAI-UF scores; • Change from Week 52/Baseline in the Uterine Fibroid Scale Quality of Life (UFS-QoL) Symptom Severity scale, and sub-scale scores and total scores. Pharmacodynamic Endpoint • Pre-dose concentration of estradiol at Week 56. Safety Endpoints • Incidence of adverse events, change in vital signs and clinical laboratory tests; • Percent change from Week 52/Baseline to Week 104 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.
Statistical Methods	Efficacy The primary efficacy endpoint of the study is the proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the randomized treatment period) as measured by the alkaline hematin method. The primary efficacy analysis is the treatment comparison between the relugolix Group A and the placebo Group B performed using a Cochran-Mantel-Haenszel (CMH) test statistic for proportions of

responders stratified by the Parent study baseline mean menstrual blood loss (< 225 mL vs ≥ 225 mL), geographic regions (North America vs Other) and the duration of relugolix exposure at Week 52/Baseline (28 weeks vs 52 weeks).

The study will be considered positive if the treatment effect for the primary endpoint is statistically significant with 2-sided p-value < 0.05. The point estimate and 2-sided 95% confidence interval (CI) for treatment difference in responder rates for the primary efficacy endpoint will be calculated.

Efficacy data will be summarized on the modified Intent-to-Treat Population (mITT) defined as all randomized patients who took at least one dose of randomized study drug. The analyses methods for efficacy endpoints are similar to those used for the Parent studies, unless otherwise specified in the Statistical Analysis Plan (SAP).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, and bone mineral density determined by DXA. Safety data analyses will be performed on the Safety Population defined as all randomized patients who receive at least one dose of randomized or open-label study drug during the study.

Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the study Week52/Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 52/Baseline and Week 104/Early Termination visits. The absolute values, change, and percent change from the Parent study Baseline, and Z-scores will be summarized by visit and study treatment group. The mean percentage change from Week 52/Baseline to Week 104 in bone mineral density and corresponding 95% CI will be provided for each treatment group.

Pharmacodynamics

Pharmacodynamic estradiol concentration data (pre-dose concentration of estradiol at Week 56) will be listed and summarized by treatment arm and visit.

Sample Size Estimation

This Randomized Withdrawal study is an extension of the OLE study. The sample size of this study will be based on approximately the number of patients who have completed either Parent study (n = 780 patients in total), and who have participated in the OLE study (approximately n = 600 patients in total assuming ~ 20% dropout rate at 6 months from the Parent studies). Assuming the proportion of responders at Week 52 in the OLE study is about 60%, it is estimated that approximately 360 patients will be responders.

With 360 patients in the randomized cohort, the study will have at least 90% power to detect a difference of 20% or greater between relugolix Group A and placebo Group B for the primary endpoint. The following assumptions are used to determine the sample size for this study:

- 2-sided type I error rate: 0.05
- Randomization: 1:1
- Responder rate for placebo Group B: 40%
- Responder rate for relugolix Group A: 60%
- Dropout rate: 20%.

Stratification factors for Randomization

- Baseline MBL volume in the Parent study (< 225 mL vs ≥ 225 mL)
- Geographic region (North America vs Europe vs Latin America vs Rest of World)
- Duration of exposure to relugolix (28 weeks vs 52 weeks).

Stratification by the 4 geographic regions (North America vs Europe vs Latin America vs Rest of World) will be used for managing the supply of investigational product. For the purpose of stratified data analyses, the 4 regions will be pooled into 2 groups (North America vs Other) where Other includes Europe, Latin America and Rest of World.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-035

PERIOD	TREATMENT PERIOD													SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3001/3002)	**Week 52/Baseline (Week 52 of OLE Study; Baseline of Study)**	**Wk 52, Day 1**	**Wks 56, 60**	**Wk 64**	**Wks 68, 72**	**Wk 76**	**Wks 80, 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104 (or Early Termination of Study Drug) [a]**	**Unscheduled [b]**	**Follow-up (~30 days after last dose of study drug) [c]**
Visit Window (days)	OLE Study Day 365 + 10		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+ 10	-	- 3 to + 18
Informed Consent	X [d]													
Review Eligibility Criteria	X													
Concomitant Medications [e]	X [f]		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X [f]					X						X	X [g]	X
Weight	X [f]					X						X	X [g]	X
Complete Physical Exam	X [f]											X		
Gynecologic Exam	X											X		
Signs and Symptoms-Directed Physical Exam [h]			X	X	X	X	X	X	X	X	X		X [g]	X
12-Lead ECG [i]	X [f]												X [g]	
Clinical Laboratory Tests [j]	X [f]			X		X						X	X [g]	X
Urinalysis	X [f]					X						X	X [g]	
Pregnancy Test (Urine)	X [f]		X	X	X	X	X	X	X	X	X	X	X [g]	X
Estradiol levels	X		X [k]											
FSH [l]						X								

PERIOD	TREATMENT PERIOD													SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3001/3002)	**Week 52/Baseline (Week 52 of OLE Study; Baseline of Study)**	**Wk 52, Day 1**	**Wks 56, 60**	**Wk 64**	**Wks 68, 72**	**Wk 76**	**Wks 80, 84**	**Wk 88**	**Wk 92**	**Wk 96**	**Wk 100**	**Wk 104 (or Early Termination of Study Drug) [a]**	**Unscheduled [b]**	**Follow-up (~30 days after last dose of study drug) [c]**
Visit Window (days)	OLE Study Day 365 + 10		± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+ 10	-	- 3 to + 18
Transvaginal Ultrasound [m]	X [f]												X [g]	
Bone Densitometry [n]	X [f]											X [o p]	X [g]	
Dispense Treatment [q]	X		X	X	X	X	X	X	X	X	X	X	X [g]	
Take Study Drug Dose in Clinic [r]			X	X	X	X	X	X	X	X	X	X	X [g]	
Daily Self-Administration of Study Drugs		X [s]	X										X [g]	
Daily Completion of Paper Bleeding Diary [t]	X												X [g]	
Dispense Feminine Products	X		X	X	X	X	X	X	X	X	X	X	X [g]	
Feminine Product Collection and Venous Blood Sample [u]	X [f]		X	X	X	X	X	X	X	X	X	X	X [g]	
Treatment Compliance	X [f]		X	X	X	X	X	X	X	X	X	X	X [g]	
SF-36 Questionnaire	X		X	X	X	X	X	X	X	X	X	X		
PGA for function and symptoms Questionnaire	X		X	X	X	X	X	X	X	X	X	X		
WPAI-UF Questionnaire	X		X	X	X	X	X	X	X	X	X	X		
UFS-QoL Questionnaire	X			X		X		X			X	X		
Adverse Event Collection	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery														X

Abbreviations: BP, blood pressure; ECG, electrocardiogram; HR, heart rate; PGA, Patient Global Assessment; SF-36, Short Form (36) Health Questionnaire; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life; WPAI-UF, Work Productivity Activity Index-Uterine Fibroid

[a] The Week 104 visit should occur on or after the 2-year anniversary of Study Day 1 of the Parent study.
[b] Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.
[c] The Safety Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit.
[d] May be signed up to 30 days prior to the Week 52/Baseline visit or during the Week 52/Baseline visit. Enrollment in MVT-601-035 is defined by administration of the first dose of MVT-601-035 study drug.
[e] Record all prescription and nonprescription drug and supplements taken from the Week 52/Baseline visit through the Safety Follow-up period.
[f] This is an MVT-601-3003 (OLE study) Week 52 procedure that serves as the Week 52/Baseline procedure for MVT-601-035 and is covered under the informed consent for the OLE study.
[g] The indicated procedure may be performed at the unscheduled visit based on the purpose of the visit (e.g., follow-up for an adverse event or abnormal laboratory test).
[h] The exam may include a gynecologic examination, if indicated based on signs and symptoms.
[i] The 12-lead ECG will be submitted for central reading at the Week 52/Baseline visit. Any subsequent ECGs performed at investigator discretion will be read locally.
[j] Clinical laboratory tests required include clinical chemistries and a complete blood count. At the Week 52/Baseline visit and Week 104 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.
[k] Pre-dose specimen drawn at Week 56 only.
[l] Specimen for FSH will be collected on patients who have been amenorrhoeic (i.e., those who have not required the use of any feminine products) since randomization.
[m] Transvaginal ultrasound, with or without transabdominal ultrasound, and with or without saline or gel contrast, is performed to determine uterine and myoma volumes and to exclude any other uterine or pelvic pathology. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Once the transvaginal ultrasound is done, a transabdominal ultrasound may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size. Results must be submitted to a central reader.
[n] Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading.
[o] This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 60 or earlier. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.
[p] Patients with a bone mineral density loss of > 7% at their Week 104/Early Termination visit relative to Parent study Baseline measurement will undergo a follow-up bone densitometry scan at 6 (± 1) months and will be contacted to question them about medications and conditions (estradiol, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.
[q] Patients will be dispensed randomized treatment at the Week 52/Baseline visit, for self-administration beginning the following day, Week 52, Day 1. Randomized treatment will be dispensed at subsequent visits until HMB (MBL ≥ 80 mL) is documented by alkaline hematin testing. When HMB has been documented, the patient will be invited for a visit to begin retreatment with open-label study drug. The timing of that visit should be within 7 days of the onset of the patient's next menses (Cycle day 1-7 where Cycle day 1 is the first day of menstrual bleeding).
[r] Patients will take the first dose of study drugs for this study once daily starting at Week 52, Day 1 (self-administered with phone follow-up). The last dose of study drug will be taken in the clinic during the Week 104/Early Termination visit.
[s] Site to call patient and confirm first dose of study drug was taken that day.
[t] Patients enter diary information on menstruation status and feminine product use.
[u] Patients will collect and return all stained and soiled feminine products to the site with the initiation of randomized study drug treatment until return of heavy menstrual bleeding (MBL ≥ 80 mL) is observed. Collection will resume following the initiation of retreatment with open-label relugolix with add back and continue until MBL is observed to be < 80 mL on two consecutive collections. When the feminine products are returned, a venous blood sample (for hemoglobin) is to be collected and sent with the products to the central laboratory conducting the alkaline hematin assessment.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

Uterine leiomyomas (often referred to as fibroids or myomas) are common benign, estrogen-dependent tumors that grow in the muscular wall of the uterus and occur in approximately 75% of women by the onset of menopause. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment [Stewart, 2001; Stewart, 2017]. The most problematic symptom for women with uterine fibroids is heavy menstrual bleeding, with menstrual periods of increased duration and volume. In women with uterine fibroids, menstrual periods can last as long as 10 to 14 days rather than the usual 5 to 7 days, and blood loss can be as high as 300 to 500 mL, with anything more than 80 mL during a given cycle considered abnormal. The heavy menstrual bleeding associated with uterine fibroids is likely caused by the increase in surface area of the uterine cavity, poor uterine contraction due to the myoma, and increased circulation, congestion, or impaired hemostasis due to hypertrophy of the endometrium near the myoma [Hapangama, 2016]. Persistent heavy menstrual bleeding can induce iron-deficiency anemia and associated fatigue and loss of energy. Heavy menstrual bleeding is a primary reason for the deterioration in the health-related quality of life assessed in patients with uterine fibroids and is a major cause of elective hysterectomy. Other symptoms include bulk symptoms, such as pain or pressure in the abdomen and pelvis due to large myoma(s), low back pain, urinary frequency or urinary tract obstruction, constipation, and pregnancy loss.

The incidence of uterine fibroids increases as women grow older, and risk factors include nulliparity, obesity, family history, black race, and hypertension. Fibroids typically arise during the reproductive years, tend to enlarge during pregnancy, and regress after menopause as these tumors are dependent upon estrogen and progesterone for their growth. Transvaginal ultrasound is used most commonly to diagnose these benign tumors, and magnetic resonance imaging, sonohysterography, and hysteroscopy are used to evaluate their size and position. The type of treatment recommended for uterine fibroids typically depends upon their size, location, the patient's age, reproductive plans, and obstetrical history. Few medical options are available for women with heavy menstrual bleeding associated with uterine fibroids, and approximately 60% of women who received medical therapy in one study underwent a surgical procedure within 2 years [Marjoribanks, 2006], suggesting many women are inadequately treated with the currently available medical therapies.

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size. However, they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, nonsteroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence of heavy menstrual bleeding after myomectomy is common, with at least 25% of women requiring additional treatment [Stewart, 2015; Marret, 2012; ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure with more than 200,000 hysterectomies performed annually in the United States (US) for uterine fibroids [Farquhar, 2002; Wu, 2007]. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel, or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection, and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the US suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012; Gliklich, 2011]. There is a great need for a safe and efficacious medicine that can decrease the symptoms of uterine fibroids so women have an alternative to myomectomy and hysterectomy.

2.2. Relugolix

The current relugolix Investigator's Brochure summarizes the nonclinical toxicology and previous human experience with relugolix. The previous human experience with relugolix includes results of phase 1 and phase 2 studies evaluating relugolix monotherapy in women with uterine fibroids or endometriosis and in men with prostate cancer, and phase 3 studies in women with uterine fibroids. The Investigator's Brochure also provides a full discussion of the safety profile of relugolix.

2.2.1. Indication

Relugolix 40 mg with estradiol 1.0 mg/norethindrone acetate 0.5 mg (relugolix with E2/NETA) is being developed as a once-daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily, and the proposed doses of estradiol and norethindrone acetate are 1.0 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly selective high-affinity small-molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Relugolix antagonizes human GnRH receptors present on gonadotropin-secreting cells of the anterior pituitary by competitively inhibiting binding of the active ligand, GnRH, to the GnRH receptors. In the absence of GnRH-stimulated secretion by the anterior pituitary, levels of LH and FSH fall rapidly, followed by a decline over a few days in estradiol and progesterone levels. Relugolix acts as a potent and highly selective antagonist for the human GnRH receptor. The affinity of relugolix for the human GnRH receptor in vitro was approximately 50-fold higher than that of GnRH in the presence of protein (40% fetal bovine serum). Transgenic knock-in mice expressing the human GnRH receptor when treated with relugolix had substantial reductions in reproductive organ weights of both female and male mice, suggesting that relugolix may suppress blood estrogen and testosterone levels, respectively. Orally administered relugolix suppressed the hypothalamic-pituitary axis in castrated cynomolgus monkeys at doses of 1 mg/kg and higher.

3. STUDY OBJECTIVES AND ENDPOINTS

The objectives of this Randomized Withdrawal study are to evaluate the long-term efficacy and safety of relugolix with E2/NETA, once daily, for up to 104 weeks in patients with uterine fibroids who have completed a total of 52 weeks of treatment including 24-week treatment period in a Parent study (study MVT-601-3001 or study MVT-601-3002) and 28-week treatment period of the OLE study and who meet the definition of responder. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.

Primary and secondary assessment of efficacy and safety assessments will be made in the following two study treatment groups:

- Group A: 52 weeks of relugolix with E2/NETA, once daily;
- Group B: 52 weeks of placebo relugolix plus a capsule of placebo estradiol/norethindrone acetate.

Week 52 of the OLE study will define the baseline for this Randomized Withdrawal study and will be used as the reference point for all changes from baseline-related endpoints. The Week 48 blood loss volume establishes responder status. Menstrual blood loss volume in this study will be compared to the threshold of 80 mL.

Objective(s)	Endpoint(s)
<u>Primary Efficacy</u>	
• To evaluate the long-term effect of relugolix with E2/NETA, once daily, compared with placebo on menstrual blood loss at Week 76 (24 weeks after randomization).	• Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the Randomized treatment period) as measured by the alkaline hematin method.

Objective(s)	Endpoint(s)
Secondary Efficacy	
• To evaluate the long-term effect of relugolix with E2/NETA, once daily compared with placebo on menstrual blood loss at 52 weeks after randomization.	• Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 104 (52 weeks of the randomized treatment period) as measured by the alkaline hematin method; • Change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period); • Percentage change from Week 52/Baseline to Week 76 and Week 104 in menstrual blood volume (during the randomized treatment period).
• To evaluate the effect of retreatment with relugolix with E2/NETA on menstrual blood loss in patients whose menstrual blood volume returned to ≥ 80 mL during the 52-week randomized period.	• Proportion of patients who responded (menstrual blood loss volume of < 80 mL) to retreatment during the retreatment period among placebo patients whose menstrual blood volume returns to ≥ 80 mL during the 52-week randomized treatment period.

• To evaluate the long-term effect of relugolix with E2/NETA at 52 weeks after randomization on the following:
  • Achievement of amenorrhea
  • Resumption of menses
  • Resumption of heavy menstrual bleeding (HMB)
  • Hemoglobin
  • Health-related Quality of Life as measured by the Short Form (36) Health (SF-36) questionnaire
  • Patient Global Assessment (PGA) for function and symptoms
  • Work and Productivity impact as measured by the Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF) questionnaire
  • Disease-specific quality of life as assessed by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) questionnaire
	The following secondary endpoints will be assessed at Week 76 and Week 104 during the randomized treatment period:
	• Proportion of women achieving or maintaining amenorrhea;
	• Proportion of women whose menses has resumed (among those who were amenorrhoeic at Week 52/Baseline);
	• Time to resumption of menses;
	• Proportion of women with menstrual blood volume ≥ 80 mL at any timepoint during the 52-week randomized treatment period;
	• Time to resumption of menstrual blood volume ≥ 80 mL;
	• Change from Week 52/Baseline in hemoglobin;
	• Change from Week 52/Baseline in SF-36 domain and summary component scores;
	• Change from Week 52/Baseline in PGA for function and symptoms score;
	• Change from Week 52/Baseline in the WPAI-UF scores;
	• Change from Week 52/Baseline in the UFS-QoL scale and sub-scale scores as well as the total score.

Objective(s)	Endpoint(s)
Pharmacodynamic	
• To characterize the pharmacodynamic (PD) effect of withdrawal from relugolix with E2/NETA	• Pre-dose concentration of estradiol at Week 56
Safety	

• To evaluate the safety and tolerability of relugolix with E2/NETA, once daily, for up to an additional 52 weeks, in patients who previously completed (responders and partial responders) the OLE study
  • Adverse events
  • Changes in bone mineral density
	• Incidence of adverse events, change in vital signs and clinical laboratory tests;
	• Percent change from Week 52/Baseline to Week 104 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This Randomized Withdrawal study (MVT-601-035) is an international phase 3 double-blind, placebo-controlled study that will enroll eligible patients with uterine fibroids who have completed the 24-week treatment period in a Parent study (study MVT-601-3001 or study MVT-601-3002) and the 28-week treatment period of the OLE study. When including treatment during the Parent study and the OLE study, patients completing this Randomized Withdrawal study will have received up to a total of 104 weeks of treatment with relugolix.

Study Population: All patients completing the OLE study with a response to treatment and consenting will be eligible to participate. Approximately 360 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. A responder is defined as a patient who demonstrates a menstrual blood loss of < 80 mL and at least a 50% reduction from Parent study baseline menstrual blood loss volume on the alkaline hematin analysis of the feminine products returned at Week 48 in the OLE study.

Objectives: The objectives of the study are to evaluate long-term efficacy and safety of treatment with relugolix with E2/NETA for up to 104 weeks (total treatment duration includes the Parent study, OLE study, and Randomized Withdrawal study).

Approximately 360 patients completing the OLE study and meeting the definition of responder and all other eligibility criteria will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA, once daily or placebo for up to 52 weeks. For patients whose menstrual bleeding returns to ≥ 80 mL (heavy menstrual bleeding), treatment with open-label relugolix with E2/NETA will be restarted. A Schedule of Activities is provided in Table 1-1.

Screening and Baseline Procedures: Screening procedures will be done on the same day as the Week 52 visit for OLE. This visit will be referred to as the "Week 52/Baseline visit". The Week 52/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments,

transvaginal ultrasound, and endometrial biopsy (only if required). When Week 52/Baseline procedures in the OLE study have been completed, the investigator will assess patient eligibility for participation in this study. The eligibility assessment will be based on data available at the Week 52/Baseline visit. No study procedures will be performed until the consent form is signed. Patients will receive the last dose of study drug in the OLE study on the day of the Week 52/Baseline visit (per the OLE protocol) and will be dispensed study drug for this Randomized Withdrawal study in the clinic after the patient is determined to be eligible for this study and has provided informed consent to participate. The first dose of study drug for the Randomized Withdrawal study will be self-administered the next morning following the Week 52/Baseline visit. Dosing will be confirmed by telephone.

Post-baseline Procedures: All post-baseline procedures are provided in the Schedule of Activities (Table 1-1).

Patients will be asked to provide feminine products for alkaline hematin analysis at each visit until the analysis confirms the return of heavy menstrual bleeding (defined as menstrual blood loss of ≥ 80 mL). The patients will then be offered retreatment with open-label relugolix with E2/NETA (latter also referred to as "add-back" in context of hormonal "add-back") with the onset of the next menses. They will resume collection of feminine products for alkaline hematin analysis until two consecutive analyses confirm resolution of heavy menstrual bleeding (menstrual blood loss of < 80 mL). Patients who experience a return of heavy menstrual bleeding (or terminate early because they have a return of heavy menstrual bleeding) but decline retreatment with open-label study drug will complete an Early Termination visit and a 30-day Safety Follow-up visit.

At the Week 104/Early Termination visit, all other patients will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA). Patients will complete the bleeding diary daily including compliance with study drug, vaginal bleeding, and use of feminine products.

The pharmacodynamic effect of withdrawal from relugolix with E2/NETA will be characterized by measuring the pre-dose concentration of estradiol at Week 56.

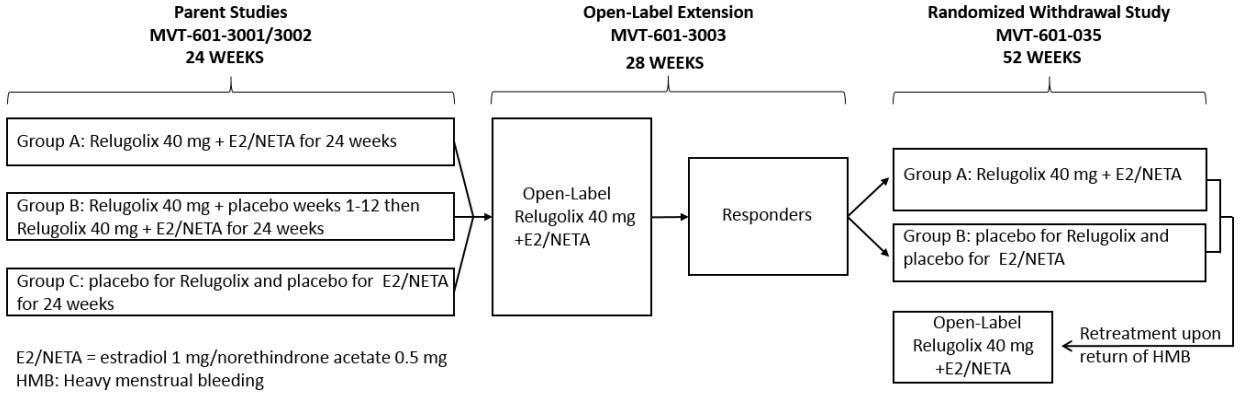
Safety will be assessed throughout the study by monitoring adverse events, vital signs and weight, physical examinations, clinical laboratory tests, and bone mineral density with DXA. Quality of life questionnaires will be completed according to the Schedule of Activities (Table 1-1).

Status of menstruation recovery will be documented at the Safety Follow-up visit (30 days after last dose of study drug). Patients whose menses have not resumed as of the Safety Follow-up visit and for whom there is no explanation for the lack of resumption (e.g., medical procedure or medications) will be contacted again by telephone 12 (± 2) weeks after the Safety Follow-up visit to determine if menses have resumed. These patients will be asked about factors that may affect the resumption of menses.

If a patient enrolls directly into another relugolix clinical study upon completion of the Week 104/Early Termination visit, then the Safety Follow-up visit and the follow-up procedures performed under this protocol may be waived.

A schematic of the MVT-601 Uterine Fibroid Program including the MVT-601-035 Study is provided in Figure 4-1.

Figure 4-1 MVT-601 Uterine Fibroid Program Schematic



4.2. Discussion of Study Design, Including Dosing

This Randomized Withdrawal study (MVT-601-035) is an extension of the 2 replicate, 24-week phase 3 Parent studies (MVT-601-3001 and MVT-601-3002) and subsequent 28-week open-label extension study (MVT-601-3003). The Parent studies and open-label extension study were designed to establish the efficacy and safety of relugolix with E2/NETA, once daily, for up to 52 weeks. This subsequent 52-week Randomized Withdrawal study provides additional efficacy and safety data for up to 104 weeks of treatment. The primary objective is to assess the long-term efficacy of relugolix with E2/NETA, once daily, for up to 104 weeks on reduction of heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. Because heavy menstrual bleeding due to uterine fibroids is a chronic condition in premenopausal women, this investigation is clinically relevant since patients are anticipated to require ongoing therapy.

In this design, the long-term efficacy of relugolix with E2/NETA will be assessed by comparing the maintenance of response in patients receiving continuous treatment to that in patients who are withdrawn from therapy. Patients who responded to open-label relugolix with E2/NETA in the OLE will be randomly assigned to continued active treatment or placebo in this study. Upon relapse, i.e., the return of heavy menstrual bleeding (MBL $\geq$ 80 mL), retreatment with open-label relugolix with E2/NETA, once daily, will be permitted. This design allows for placebo-controlled assessment of maintenance of efficacy while minimizing the duration of time in which symptomatic patients are without treatment. The effect of active treatment will be demonstrated by observing the difference in response between continued active treatment and placebo groups.

This design also affords the opportunity to assess the effectiveness of retreatment. This is important because, in clinical practice, interruption of treatment for variable lengths of time may occur due to circumstances such as poor compliance, desire to conceive, reimbursement issues, or intercurrent illness or surgery. Patients in this Randomized Withdrawal study who are given retreatment will be assessed to evaluate whether improvement in heavy menstrual bleeding can be recaptured.

The dose of relugolix for this Randomized Withdrawal study is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar

to those in the group of women treated with leuprolide subcutaneous injection (3.75 mg). Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40 mg dose provided the greatest reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development.

The 40 mg dose has been used in two phase 3 studies in Japan. One study demonstrated that relugolix 40 mg administered once daily to women experiencing heavy menstrual bleeding due to uterine fibroids reduced menstrual blood loss similar to leuprolide. The second study compared 40 mg relugolix to placebo in women having pain symptoms associated with uterine fibroids. The study included women with a Numerical Rating Scale (NRS) of score of ≥ 4 in the menstrual cycle prior to randomization. The proportion of subjects without pain symptoms (NRS = 0) during the 28 days before the final dose of study drug was higher in the relugolix 40 mg group (48.5%) than in the placebo group (3.1%).

However, data on bone mineral density from DXA scanning in both the phase 2 and phase 3 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that limits dosing of relugolix to short term use only. To mitigate this known adverse consequence of estrogen suppression, relugolix is given with E2/NETA in phase 3 clinical studies, including this study. Estradiol 1.0 mg with norethindrone acetate 0.5 mg is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily led to less bone mineral density loss, these doses did not provide adequate relief from heavy menstrual bleeding in a high enough percentage of women to move forward into phase 3 clinical development. Additionally, based on the DXA data from the phase 2 study, these lower doses are not expected to prevent bone mineral density loss in a significant majority of women over 52 weeks of treatment.

The co-administration of hormonal add-back therapy with relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 104 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in heavy menstrual blood loss. It is well known that bone is exquisitely sensitive to estrogen and low-doses of supplemental estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2017]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2015; Lee, 2016; Franke, 2000]. The estradiol/norethindrone acetate combination proposed for evaluation in combination with relugolix in this Randomized Withdrawal phase 3 study is currently approved in the US as long-term hormone replacement

therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2017].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix with E2/NETA demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, a range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back hormonal therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2017]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this Randomized Withdrawal study (1.0 mg and 0.5 mg, respectively) are also used in the Parent studies (MVT-601-3001 and MVT-601-3002) and the OLE study (MVT-3003). This hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women in well-designed phase 2 and phase 3 studies. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 double-blind, placebo-controlled Randomized Withdrawal study will assess long-term efficacy and safety of relugolix with E2/NETA, once daily, for the reduction of heavy menstrual bleeding associated with uterine fibroids, and for mitigation of bone mineral density loss and other side effects associated with a hypoestrogenic state such as hot flushes.

This Randomized Withdrawal study will provide information on long-term efficacy and safety data for an additional 52 weeks of treatment, providing approximately 2 years of efficacy and safety data from the women with uterine fibroids treated with relugolix in the Parent studies (MVT-601-3001 and MVT 601-3002) and the OLE (MVT 601-3003) study.

4.3. Selection of Study Population

The study population will include approximately 360 responders who have completed the 24-week treatment period in a Parent study (Study MVT-601-3001 or Study MVT-601-3002) and the 28-week treatment period of the OLE study with a response to treatment and meet all eligibility criteria for this study.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety.

Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for enrollment in this study only if all of the following inclusion criteria are met at the time of the Week 52/Baseline visit:

1. Completed the OLE study (MVT-601-3003);
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-035;

   Note: Procedures conducted as part of the OLE study that also serve as baseline procedures for this study may be done under the informed consent for the OLE study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including the Safety Follow-up period;
4. Is a responder: Has a menstrual blood loss of < 80 mL AND at least a 50% reduction from the Parent study baseline based on the results of the alkaline hematin testing performed on the feminine products returned at the Week 48 visit of the OLE. Results from Week 44 may be used if Week 48 data is unavailable;
5. Has a negative urine pregnancy test at the Week 52/Baseline visit;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the treatment period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 24 weeks prior to the Week 52/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 16 weeks prior to the Week 52/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (e.g., Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

4.3.2. Exclusion Criteria

None of the following criteria may be true for a patient to be eligible for enrollment into this study:

1. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-

guided focused ultrasound for fibroids, or endometrial ablation for abnormal uterine bleeding at any time during the Parent study or OLE study;

2. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (e.g., bilateral hip replacement or spinal hardware in the lumbar spine);
3. Anticipates use of any prohibited medications as detailed in Section 5.9.1;
4. Has developed any contraindication to treatment with estradiol or norethindrone acetate, including:
   a. Known or suspected breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism;
   d. Active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. Porphyria;
5. Has current active liver disease from any cause;
6. Has a new diagnosis of a systemic autoimmune disease (e.g., systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;
7. Had any of the following clinical laboratory abnormalities at the OLE study Week 48 visit or any subsequent visit:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
   c. Hemoglobin < 8 g/dL despite iron supplementation;
8. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 4 weeks after the last dose of study drug, or plans to donate ova during the study period or within 8 weeks after the last dose of study drug;
9. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor.
10. Met a withdrawal criterion in the OLE study.

4.4. Method of Assigning Patients to Treatment Group and Patient ID Number

Eligible patients who sign consent will be identified with the same Patient Identification Number assigned to the patient during the OLE study. All patients completing the OLE study with a

response to treatment and consenting will be eligible to screen. Once eligibility is confirmed, they will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA, once daily or placebo for up to 52 weeks.

4.5. Removal of Patients from Therapy

Completion of the Week 104 visit with appropriate safety follow-up defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 104 visit on the Schedule of Activities; Table 1-1) and will have a follow-up visit to assess safety approximately 30 days after the end of study drug treatment (i.e., after the patient's last dose of study drugs).

The following safety and/or compliance events will result in the removal of patients from therapy either permanently or until the etiology of the problem has been identified and resolved:

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to an undue risk to the patient if dosing continued;
- If it is discovered after enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- If an iron deficiency anemia related to heavy menstrual bleeding develops with a hemoglobin < 8g/dL and is unresponsive to iron supplementation;
- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the Parent study Baseline at lumbar spine, total hip, or femoral neck based on the OLE study Week 52 DXA assessment of bone mineral density;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; or missing multiple study visits;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous noncompliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should make at least 3 documented attempts to contact the subject by telephone, or if necessary by certified letter so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.6. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded. Patients must agree to use nonhormonal contraception throughout the study unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 52/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™) at least 4 months prior to the Week 52/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Has a nonhormonal intrauterine device (e.g., Paragard®) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as described below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of contraception for whom none of the above methods apply are:

- Condom (male or female condom) with or without spermicide (cream, spray, foam, gel, suppository, or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm with signing of the consent form that they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 2 months following the last dose of study drug.

A patient may start hormonal contraception 4 weeks after her last study dose of study drug provided her menstrual cycle has returned.

Urine pregnancy tests will be performed at monthly intervals during the study (including prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

Approximately 360 patients completing the OLE study and meeting the definition of responder and meeting all other eligibility criteria will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA (relugolix with add-back) or placebo for up to 52 weeks.

- Group A: 52 weeks of oral relugolix with E2/NETA, once daily;
- Group B: 52 weeks of placebo relugolix plus a capsule of placebo estradiol/norethindrone acetate.

The placebo relugolix tablet is manufactured to match the relugolix tablet in size, shape, and color. The placebo capsule is designed to match the over-encapsulated estradiol/norethindrone acetate active product in size, shape, color, and odor.

After randomization, if the alkaline hematin analysis confirms the return of heavy menstrual bleeding (defined as menstrual blood loss of ≥ 80 mL) the patient will be offered retreatment at their next visit with open-label relugolix with add-back for the remainder of the treatment period.

Descriptions of all study drugs are provided in Table 5-1.

Table 5-1 Description of MVT-601-035 Study Drugs

Name of Investigational Product	Blinded and Open-Label Relugolix	Relugolix Placebo	Blinded Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo	Open-Label Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material	A Swedish orange capsule with placebo back-fill material	Round, white, biconvex, film-coated tablet
Dosage Form	Tablet	Tablet	Capsule	Capsule	Tablet
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / Norethindrone acetate 0.5 mg	0 mg	Estradiol 1.0 mg / Norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks	Oral once daily for up to 52 weeks

5.2. Identity of Investigational Product

Relugolix has the chemical name 1-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidin-6-yl}phenyl)-3-methoxyurea.

Estradiol (1.0 mg)/norethindrone acetate (0.5 mg) is a fixed-dose combination product.

5.2.1. Product Characteristics

Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients.

The fixed-dose combination tablet of estradiol 1.0 mg/norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

5.3. Randomization and Stratification

Patients are randomized 1:1 ratio to blinded treatment with oral relugolix with E2/NETA (relugolix with add-back) or placebo. Stratification factors for randomization are as follows:

- Baseline MBL volume in the Parent study (< 225 mL vs ≥ 225 mL)
- Geographic region (North America vs Europe vs Latin America vs Rest of World)
- Duration of exposure to relugolix (28 weeks vs 52 weeks).

5.4. Directions for Administration

The study drugs should be taken in the fasted state (water, tea, or coffee are allowed) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study drugs should be taken as close as possible to the same time of morning each day.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated using adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Patients may subsequently be restarted on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20 – 25°C (68 – 77^0F) (with excursions permitted ± 5°C) to 15 - 30°C (59 - 86^0F) permitted until it is used or returned to the sponsor (or designee). Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

Study drug will be labeled with the study protocol number, lot/batch number, expiry date, contents, directions for use, storage directions, clinical study statement, and any other labeling required by regulatory bodies in the study locations and will list Myovant Sciences GmbH as the sponsor. Patients will be instructed to store study drug at room temperature out of the reach of children.

All labels for relugolix and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

For randomized treatment, relugolix 40 mg will be supplied to the study site in blister cards. It will be co-packaged with the estradiol/norethindrone acetate. Open-label relugolix will be supplied in a bottle, and the open-label estradiol/norethindrone acetate will be supplied in a dial pack.

5.7. Blinding

During the double-blind Randomized Treatment and through the Safety Follow-up period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes. The blind will be maintained during assessment of pharmacodynamic testing. Estradiol and FSH concentrations will be reported to the sponsor only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment and the decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator. However, the investigator should attempt to contact the medical monitor or appropriate study personnel to discuss options before unblinding the patient's treatment assignment unless the urgency of the medical situation precludes this. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the investigator must

notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

The sponsor (or designee) may unblind the treatment assignment for any patient with a serious adverse event.

For randomized patients whose menstrual blood volume returns to ≥ 80 mL during the 52-week randomized treatment period, therefore, will get retreatment with oral relugolix with E2/NETA, their randomized treatment assignment information is blinded during the 52-week randomized treatment period for all patients, investigators, and sponsor staff or representatives involved in the conduct of the study.

5.8. Study Drug Accountability and Treatment Compliance

Patients should bring all unused and used study drugs to each study visit. Study drug accountability will be conducted, and results will be recorded. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Prior and Concomitant Medications and Non-Drug Therapies

5.9.1. Prohibited Medications

Table 5-2 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 5-2 are prohibited at any time during the study through the to the Safety Follow-up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-2 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-Androgens	danazol	
Anti-convulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	All other anticonvulsants are allowed.
Aromatase Inhibitors	anastrozole letrozole	

Drug Class	Examples	Comments
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine Devices	Levonorgestrel intrauterine system	
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin clopedigril tranexamic acid vitamin k preparations factor Xa inhibitors	
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use (at screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study is prohibited. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration ($\leq$ 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.

Drug Class	Examples	Comments
P-glycoprotein Inducers	avasimibe carbamazepine phenytoin rifampin St. John's Wort tipranavir/ritonavir	For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol[g] clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelor verapamil	For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone

a. Roxithromycin is allowed
b. All other angiotensin converting enzyme inhibitors are allowed
c. Tacrolimus is allowed
d. Amlodipine and nifedipine are allowed
e. Fluconazole is allowed
f. Integrase inhibitors are allowed
g. Metoprolol and atenolol are permitted

5.9.2. Permitted Medications

All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.

5.9.2.1. Analgesics

From the Week 52/Baseline visit to the Week 104/Early Termination visit, the use of analgesics for uterine fibroid-associated pain should be in accordance with the local standard of care and at the discretion of the investigator.

5.9.2.2. Iron Therapy

Women who enter the Randomized Withdrawal study on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron-deficiency anemia during the study, defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.9.3. Prohibited Non-Drug Therapies

Surgical and other interventional treatment of uterine fibroids is prohibited from the Week 52/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1-1). Study procedures are briefly described in Section 6.5. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Table 1-1). The study is divided into 2 periods: Treatment period (Table 1-1) and Safety Follow-up period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Treatment Period (Week 52/Baseline to Week 104)

As denoted in the Schedule of Activities (see Table 1-1), certain Week 52 visit procedures in the OLE study will serve as the Week 52/Baseline procedures for patients who are interested in participating in this Randomized Withdrawal study, and these Week 52 procedures will be performed under the informed consent for the OLE study.

Patients will be required to sign an informed consent form for the Randomized Withdrawal study and will be eligible if they meet all the eligibility criteria.

Once eligibility is determined, all additional Week 52/Baseline visit procedures described in the Schedule of Activities (see Table 1-1) that were not performed as part of the Week 52 visit of the OLE study will be completed. These include the following:

- Informed consent;
- Record concomitant medications;
- Dispense study treatment;
- Dispense feminine products;
- Record adverse events, if any.

Patients will record vaginal bleeding and feminine product use in a paper diary each day. Safety monitoring including physical examination, pregnancy tests, and adverse event assessment will

occur at each visit. Additional safety assessments will be performed as described in the Schedule of Activities (see Table 1-1). Bone densitometry will occur at the Week 52/Baseline, and Week 104/Early Termination visits. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 52/Baseline visit.

Study drug compliance will be reviewed at each visit.

Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 52/Baseline and Week 104/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether the patient fasted for the chemistry and lipid testing.

Patients will be randomized 1:1 to blinded treatment with oral relugolix with E2/NETA, once daily, or placebo beginning on the day following the Week 52/Baseline visit and continuing through the Week 104 visit.

Patients will receive their last dose of study drug in the OLE study on the day of the Week 52/Baseline visit (as per the OLE study protocol), and the patient will be provided blinded study drug to begin dosing the following day. The first dose of study drug will be self-administered the next morning following the Week 52/Baseline visit. After the Week 52/Baseline visit, a phone call will occur on Week 52 Day 1 (+ 2 days) to document the time of self-administration of the first dose of study drugs and record any reported adverse events. On-treatment study visits will occur every 4 weeks for a total of 104 Weeks. With the initiation of randomized treatment, patients will collect all stained/soiled feminine products and at the study visits return their feminine products for alkaline hematin testing. A venous blood sample (for hemoglobin) must be collected each time feminine products are returned and sent to the central laboratory conducting the alkaline hematin assessment. If the patient is having cyclic bleeding, the site must document the start and stop dates of the patient's menses corresponding to the collected feminine products. The paper diary recording vaginal bleeding and feminine product use should be reviewed at each visit to assess compliance with feminine product collection.

When the alkaline hematin analysis indicates MBL ≥ 80 mL, the patient will be asked to return with onset of the next menses, no later than cycle day #7 (where cycle day #1 is the first day of menstrual bleeding), to begin retreatment with open-label relugolix with E2/NETA. The timing of this visit may necessitate an unscheduled visit. The final dose of randomized treatment should be self-administered by the patient the day prior to presenting for retreatment. The first dose of retreatment with open-label relugolix with E2/NETA will be administered at the clinic visit. Feminine products do not need to be collected with the episode of menstrual bleeding associated with the initiation of retreatment, but once the episode is complete, all stained/soiled feminine products must be collected and returned at subsequent visits for alkaline hematin analysis until MBL < 80 mL is observed for two consecutive collections.

6.3. Early Termination Visit and Safety Follow-up Visit

All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104; however, for patients whose last dose of study drug is during Week 56, bone densitometry does not need to be

performed. However, densitometry may be performed at the investigator's discretion as an aid to adverse event follow-up.

Patients who experience a return of heavy menstrual bleeding (or terminates early because they have a return of heavy menstrual bleeding) but decline retreatment with open-label study drug will complete an Early Termination visit and a 30-day Safety Follow-up visit.

Patients (including those who complete the Week 104 visit and those who withdraw early from this study) will have a follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for uterine fibroids, whichever occurs first. However, the Safety Follow-up visit may be waived for patients who enroll directly into another relugolix clinical study upon completion of the Week 104 visit.

The Safety Follow-up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (Table 1-1) for individual study visit procedures during the Safety Follow-up visit.

6.4. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, to initiate retreatment, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance, and dispensation, etc., may be conducted as clinically indicated. See the Schedule of Activities (Table 1-1) for tests that may be performed, as indicated by the reason for a visit, at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform transvaginal ultrasound endometrial biopsy, or DXA, unless urgently indicated.

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Bleeding Diary

All women enrolled in the study will be provided with a paper bleeding diary along with instructions for its use. Patients will complete the diary daily including compliance with study drug, vaginal bleeding, and use of feminine products.

6.5.1.2. Menstrual Blood Loss as Assessed by the Alkaline Hematin Method

The volume of menstrual blood loss is measured in milliliters using the alkaline hematin method [Hallberg, 1964]. The method involves pummeling used feminine products in a solution and measuring the resulting hematin absorbance against calibration curves. The method is validated in accordance with current FDA Guidance for Method Validations and is an accepted quantitative clinical endpoint for the assessment of heavy menstrual bleeding. The site staff will provide collection kits with standardized and validated feminine products to patients for the collection and assessment of those products to determine menstrual blood loss.

The feminine products will be dispensed and all stained/soiled products will be collected at each visit starting with the initiation of randomized study drug treatment. Product collection will continue at each visit unless heavy menstrual bleeding (MBL ≥ 80 mL) is observed. Collection will resume following the initiation of retreatment with open-label relugolix with E2/NETA and continue until MBL is observed to be < 80 mL on two consecutive collections. If the patient is having cyclic bleeding, the site must document the start and stop dates of the patient's menses. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to with the products to the the laboratory for the alkaline hematin analysis. Details regarding materials, process, and requirements for the menstrual blood loss collection are provided in the Study Reference Manual.

6.5.1.3. Transvaginal and Transabdominal Ultrasound

Transvaginal ultrasound will be performed for all subjects at the Week 52/Baseline visit as a part of the OLE study (MVT-601-3003). Once the transvaginal ultrasound is complete, a transabdominal ultrasound (with or without saline or gel contrast) may also be performed if the uterus cannot be adequately imaged on transvaginal ultrasound (e.g., due to enlarged size). Transvaginal ultrasound, with or without transabdominal ultrasound, is performed to determine uterine and myoma volumes. A single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device, as far as possible, to avoid inter-observer and inter-device variations. This single operator should be the same person, if possible, as previously assigned to the patient during her participation in the Parent study.

On the assumption that the uterus and myoma are spheroids, uterine and myoma volumes are calculated using the formula:

Uterine or myoma volume = $D1 \times D2 \times D3 \times \pi / 6$
Where:

- D1 = the longest diameter of the myoma or uterus (unit of length: cm)
- D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
- D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. Any ultrasounds performed after the Week 52/Baseline visit must be read locally.

6.5.1.4. Health Survey Standard (SF-36)

The Health Survey Standard (SF-36) is a validated 36-item questionnaire which measures quality of life across eight health domains that can be combined into a physical and a mental summary component score. (see Appendix 1). The SF-36 has a 4-week recall period and will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). With the exception of the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.1.5. Patient Global Assessment (PGA) for Function and Symptoms

The PGAs for Function and Symptoms are completed by the patient; they are based on a 5-point Likert scales and have a 4-week recall period (see Appendix 2). The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). Except for the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.1.6. Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF)

The Work Productivity Activity Impairment-Uterine Fibroids (WPAI-UF) is a validated instrument used to measure impairments in work and activities, which has been adapted for uterine fibroids (see Appendix 3). The WPAI-UF will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). Except for the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.1.7. Uterine Fibroid Symptom and Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QoL) is a validated instrument used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). The UFS-QoL will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Table 1-1). Except for the Week 52/Baseline visit, patients will answer these questions before other types of study procedures are performed.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

Patients should have weight measured while wearing indoor clothing and with shoes removed.

6.5.2.2. Vital Signs

Vital signs, including blood pressure, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest and will include systolic and diastolic blood pressure and pulse rate.

6.5.2.3. Physical and Gynecologic Exams

A complete physical examination will include examinations of head, ears, eyes, nose, mouth, thyroid, skin, heart and lung, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from previous assessments. The gynecologic examination will include breast and pelvic exams.

6.5.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities (see Table 1-1). Laboratory requisition forms must be completed, and samples must be clearly labeled with the Patient Identification Number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all laboratory tests will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 6-1.

Table 6-1 Clinical Laboratory Tests

<table>
<tr><th>Chemistry</th><th>Hematology</th><th>Urinalysis</th></tr>
<tr><td rowspan="3">Potassium
Chloride
Bicarbonate
Blood Urea Nitrogen
Creatinine
Glucose
Calcium
Phosphate
Magnesium
Sodium
Albumin
Hemoglobin A1c
Creatine Kinase
Bilirubin Total
Alanine Aminotransferase
Aspartate Aminotransferase
Gamma-Glutamyl Transferase
Alkaline phosphatase</td><td>White Blood Cell (WBC) Count
WBC Differential
Red Blood Cell Count
Hemoglobin
Hematocrit
Mean Corpuscular Volume
Platelet Count
Red Blood Cell (RBC) morphology</td><td>Protein
Glucose
Blood
Urobilinogen
Bilirubin
Color and Clarity
pH
Leucocyte Esterase

Ketones
Nitrite
Specific Gravity
Urine Microscopy (reflex testing based on abnormal urine analysis)</td></tr>
<tr><td>Lipids</td><td>Pregnancy</td></tr>
<tr><td>Total Cholesterol
Low Density Lipoprotein
High Density Lipoprotein
Triglycerides</td><td>Pregnancy test (human chorionic gonadotropin)</td></tr>
<tr><td>Hormones</td><td colspan="2" rowspan="2"></td></tr>
<tr><td>Estradiol
FSH</td></tr>
</table>

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally.

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal and clinically significant results should be reported as adverse events.

The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

To maintain blinding, concentrations of hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.5.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at Week 52/Baseline visit in this study, as well as if needed to evaluate any signs or symptom that require an ECG to assess. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant. Any ECGs performed after the Week 52/Baseline visit will be read locally.

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3, and L4), total hip, and femoral neck (same leg within each patient). Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will be used at each site and operated in the same scan mode for all scans for each patient. This should be the same as used for the patient during the OLE study. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual subjects will be monitored by a central radiology laboratory over the course of the study.

Patients who experience a bone mineral density loss of $\geq$ 7% from the Parent study baseline at any of the anatomical sites assessed will be discontinued from the study and will undergo another bone densitometry scan as described below. Patients should be assessed for secondary causes of bone loss and followed-up further if not improving on 6 months follow-up scan unless an alternative etiology has been identified.

Patients with a bone mineral density loss of ≥ 7% at lumbar spine, total hip, or femoral neck at their Week 104/Early Termination visit relative to Parent study baseline measurement will undergo another bone densitometry scan at 6 (± 1) months and will be contacted to obtain information about medications and conditions (e.g., pregnancy) that might affect bone mineral density through the time of the follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.

6.5.2.7. Status of Menstruation Recovery

If the first menstruation after the end of study treatment administration is observed before the Safety Follow-up visit, the date of onset of the first menstruation is recorded in the electronic case report form (eCRF). Patients whose menses has not resumed as of the Safety Follow-up visit for whom there is no explanation for the lack of resumption (e.g., medical procedure or medications) will be contacted again by telephone 3 (± 0.5) months after the Safety Follow-up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

7. SAFETY CONSIDERATIONS

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), clinical laboratory tests, ECGs, and bone mineral density assessments.

7.1. Adverse Event Definitions

7.1.1. Adverse Event

Adverse event: An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Events meeting the definition of an adverse event include:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (e.g., for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and

- An investigational abnormality (e.g., laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

Events that do not meet the definition of an adverse event include:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event;
- Pre-existing diseases or conditions present or detected before the start of study drug administration that do not worsen;
- Situations where an untoward medical event has not occurred (e.g., planned hospitalization for an elective procedure, with elective defined as known or planned at the time of signing of the informed consent);
- Events of heavy menstrual bleeding, as heavy menstrual bleeding is quantified as an efficacy endpoint, unless meets seriousness criteria.

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below. No toxicity-related dose reductions of study drug are permitted; however, study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. The study drug may be restarted if deemed safe for the patient by the investigator.

7.1.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death;

b. Is life-threatening;

   NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been admitted to a hospital, independent of the duration of that hospitalization. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization

for elective treatment of a pre-existing condition that did not worsen from the Week 52/Baseline visit is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect;

f. Important medical events that jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local institutional review board (IRB) or institutional ethics committee (IEC).

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about adverse event occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

The patient's answers to study questionnaires will not be used as a primary means to collect adverse events, however they should be reviewed by the study site personnel and the study monitors. Should the investigator or site staff become aware of a potential adverse event through the information collected with these instruments, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up, if it is determined that an adverse event not previously reported has been identified, normal reporting requirements should be applied.

All patients who experience an adverse event will be evaluated at appropriate time intervals until the event resolves or has stabilized or become chronic. At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted.

All adverse events, whether related to the study drug treatment, must be fully and completely documented on the adverse event case report form and in the patient's source documents. In

addition, any adverse event resulting in permanent treatment discontinuation must be recorded on the appropriate case report form as well as documented in the patient's source documents. Adverse event terms should include a diagnosis, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual adverse event.

Overdose and pregnancy in the patient will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Safety Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Table 1-1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

Reporting instructions for serious adverse events are provided in Section 7.6.

7.3. Assigning Causal Relationship to Study Drug

The reasonable possibility of the relationship of an adverse event to study drug(s) is to be assessed with careful medical consideration at the time of evaluation of an adverse event. The following definitions are to be used for the relationship of the adverse event to study drug:

- **Probably related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on readministration (rechallenge) or withdrawal (dechallenge).
- **Possibly related**: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

All adverse events, whether related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

7.4. Assigning Severity Rating for Adverse Events

Severity describes the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance, such as a

severe headache. This is not the same as "serious," which is based on patient/event outcome or action taken.

The investigator must determine the severity of each adverse event according to the National Cancer Institute CTCAE. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

Table 7-1 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life-threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

Adverse event severity should be recorded in the appropriate section of the adverse event case report form and in the patient's source documents.

7.5. Adverse Events of Clinical Interest Reporting

Adverse events of clinical interest in this study are defined as any increase in ALT or AST ≥ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the open-label Treatment period or Safety Follow-up period should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet serious adverse event criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 5.

7.5.1. Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities

Hepatic enzymes will be monitored in accordance with FDA drug-induced liver injury guidelines [FDA, 2009].

If the following liver test abnormalities develop, study drug should be withheld immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status), and the event reported as a serious adverse event:

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or

- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** INR > 1.5; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

Rechallenge may be considered if an alternative cause for the abnormal liver tests (ALT, AST, total bilirubin) is discovered and the laboratory abnormalities resolve to normal or Week 52/Baseline values. The investigator and sponsor must discuss and agree with any decision to rechallenge.

Rechallenge should not occur when the etiology of the liver test abnormalities is considered possibly drug-induced.

7.5.2. Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities

Study drug treatment should be discontinued permanently if all of the following 4 criteria are met (i.e., potential severe drug-induced liver injury/Hy's law case):

1. AST or ALT increases to ≥ 3 x ULN; AND
2. Total bilirubin increases to > 2 x ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 x ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (e.g., hepatitis A/B/C/D/E, Epstein Barr virus);
   - Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   - Alcoholic hepatitis;
   - Nonalcoholic steatohepatitis;
   - Autoimmune hepatitis.

If an alternative cause for hepatotoxicity is identified, then it should be determined (based on the severity of the hepatotoxicity or event) whether study drug treatment should be withheld or permanently discontinued as appropriate for the safety of the patient.

7.6. Serious Adverse Event Reporting

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 contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the serious adverse event report form and is as follows:

Send completed Safety Report Forms to IQVIA RDS Inc:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
All study sites	PPD	PPD

For questions on Serious Adverse Event/Adverse Event of Clinical Interest reporting, please call:

- North/South America: PPD
- Europe, Asia, Pacific, and South Africa: see region-specific phone numbers accompanying the Safety Report Form

The initial report should include:

- Study number (MVT-601-035);
- Site address and number;
- Investigator name;
- Patient Identification Number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity);
- Causal relationship to the study drug.

If the patient died, the report should include the cause of death as the event term (with death as outcome) and whether or not the event leading to death was related to study drug treatment, as well as the autopsy findings if available.

Do not delay reporting a suspected serious adverse event in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. All serious adverse events will be followed until resolution, until the event has stabilized, and/or reached a new baseline. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

7.7. Study Drug Overdose Management

The medical monitor must be contacted in the event of any study drug overdose.

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study patient, at a dose above that assigned to that individual patient according to the study protocol.

For this study, any dose of relugolix > 80 mg within a 24-hour window is an overdose and any dose of estradiol/norethindrone acetate > 2 x the protocol dose is an overdose (i.e., more than 2 capsules taken within a 24-hour window). There is no known antidote for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for pharmacokinetic analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

The medical monitor, in consultation with the investigator, will make decisions regarding patient status and potential dose interruptions, based on the clinical evaluation of the patient.

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

Pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the pregnancy report forms and contact information in Section 7.6. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, and neonatal data, etc., should be included in pregnancy report form, as available.

The investigator will follow the medical status of the mother, as well as the fetus, and will report the outcome to the sponsor.

7.9. Vital Signs, Physical Examinations, Clinical Laboratory Tests, Electrocardiograms, and Bone Mineral Density Measures

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, weight, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, arthralgia, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on the heavy menstrual bleeding associated with uterine fibroids. Hormonal add-back therapy with estradiol/norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

Potential risks that may be associated with relugolix treatment in women, based on nonclinical data and data available for similar compounds, include drug interactions, cardiovascular effects (corrected QT interval [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD),

reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator's Brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 7-2.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of estradiol/norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the Parent studies.	Bone mineral density will be monitored at the Week 52/Baseline and Week 104/Early Termination visits with specified discontinuation and follow-up criteria, and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the Parent studies.	12-lead ECG at the Week 52/Baseline and Week 104/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzyme increases Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN.	Abnormal liver test results (AST or ALT > 3 x ULN) that develop during the Treatment period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the Parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable nonhormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.
Risk of Estradiol 1.0 mg/Norethindrone Acetate 0.5 mg Estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignancies, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the Parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 52/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

Sponsor personnel or designee(s) will visit the study site if necessary prior to initiation of the study to review information about the study drug, protocol requirements, eCRFs, monitoring requirements, reporting of serious adverse events, and to ensure a full understanding of the Study Reference Manual with the site personnel.

8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (e.g., patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

Management of clinical data will be performed in accordance with applicable sponsor-approved standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data).

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced, respectively.

The investigator will retain original source documents and the sponsor will receive eCRF-required data as electronic datasets. Patient initials will not be collected or transmitted to the sponsor.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A Statistical Analysis Plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patient's study treatment assignments.

All hypothesis tests and confidence intervals will be 2-sided at an alpha level of 5%. Methodology to be used to maintain study-wide type I error rate of 5% testing across primary and key secondary endpoints will be described in the SAP.

All efficacy and safety measures over the course of the study will be presented. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

The final analysis of efficacy and safety data will occur after approximately 360 patients (projected to be responders from the open-label extension study MVT-601-3003) who have been randomized and have had the opportunity to complete Week 104 visit or through the 30-day Safety Follow-up visit.

9.1. Randomization Methods

This is an international phase 3 Double-Blind, Placebo-controlled, Randomized Withdrawal study that will enroll eligible patients with uterine fibroids who have completed the 24-week treatment period in a Parent study (Study MVT-601-3001 or Study MVT-601-3002) and the 28-week treatment period of the OLE study. Patients completing the OLE study and meeting the definition of responder will be randomized 1:1 into two different treatment groups:

- Group A: 52 weeks of oral relugolix with E2/NETA, once daily;
- Group B: 52 weeks of placebo relugolix plus a capsule of placebo estradiol/norethindrone acetate.

Randomization will be stratified by the following factors:

- Geographic Region: North America vs Europe vs Latin America vs Rest of World;
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL; and
- Duration of relugolix exposure prior to randomization (28 weeks vs 52 weeks).

The four stratification levels (North America vs Europe vs Latin America vs Rest of World) for geographic region considered for randomization take drug supply monitoring into consideration. For the purpose of stratified data analyses, the 4 regions will be pooled into two groups (North American vs Other) where Other includes Europe, Latin America and Rest of World.

Statistical analyses for efficacy endpoints will incorporate these stratification factors unless otherwise specified.

9.2. Analysis Populations

The modified Intent-to-Treat (mITT) Population will consist of all patients randomized to treatment who have taken at least one dose of study treatment. The mITT Population will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the mITT Population who have no relevant major protocol violations, defined as a subset of all major protocol violations (details will be provided in the Statistical Analysis Plan). The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the mITT Population.

This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least one dose of study treatment.

9.3. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the mITT Population according to the randomized treatment assignment, and stratified analyses will be stratified by the randomization stratification factors. If the group of patients from any of the individual randomization stratification factors comprises less than 10% of the entire mITT population, this stratification factor will be ignored for stratified analyses.

9.3.1. Primary Efficacy Endpoint

The primary endpoint of the study is the proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 76 (24 weeks of the randomized treatment period) as measured by the alkaline hematin method. The primary endpoint of responder rate will be evaluated using the mITT Population.

Week 52 of the OLE study will define as the baseline for this Randomized Withdrawal study and will be used as the reference point for all changes from baseline-related endpoints. Although responder status is based on Week 48 of the OLE study, the menstrual blood loss (MBL) volume at the Week 52 period of the OLE study will establish the patient's baseline for evaluation of menstrual blood loss during the 52-week randomized treatment period of the study.

9.3.1.1. Primary Analysis

The primary hypothesis for the primary efficacy endpoint to be tested in this study is relugolix (Group A) is superior to placebo (Group B) with respect to the proportion of responders at Week 76 (24 weeks after randomization) based on the MBL volume analyzed by alkaline hematin method:

Null hypothesis H_{01}: $\pi^R \leq \pi^P$ vs Alternative hypothesis $H_{a1:}$ $\pi^R > \pi^P$

where π^R and π^P are the responder rates for relugolix and placebo groups, respectively.

The primary efficacy analysis is the treatment comparison between the relugolix Group A and the placebo Group B performed using a Cochran-Mantel-Haenszel (CMH) test statistic for proportions of responders stratified by baseline mean menstrual blood loss in the Parent study (< 225 mL vs ≥ 225 mL), geographic region (North America vs Other) and the duration of relugolix exposure prior to randomization (28 weeks vs 52 weeks).

The study will be considered positive if the treatment effect for primary endpoint is statistically significant with 2-sided p-value < 0.05. The point estimate and 2-sided 95% confidence interval (CI) for treatment difference in responder rates for the primary efficacy endpoint will be calculated.

9.3.1.2. Subgroup Analyses

Subgroup analyses of the primary efficacy endpoint comparing Group A versus Group B will be performed to determine whether treatment effect is consistent across clinically meaningful subgroups. The difference in responder rates and their 95% confidence intervals will be displayed in a forest plot. Subgroups will include but not be limited to the following: baseline MBL volume in the Parent study (< 225 mL vs ≥ 225 mL), geographic region (North America vs Other), duration of exposure to relugolix prior to randomization (28 weeks vs 52 weeks) as well as other baseline subgroups such as age, and race. Details are provided in the Statistical Analysis Plan.

9.3.1.3. Sample Size Estimation

Because this is an extension of the OLE study, the sample size of this study will be based on approximately the number of patients who have completed a Parent study (n = 780 patients in total), and who participated in the OLE study (n = 600 patients in total assuming about 20% dropout rate at 6 months from the Parent studies). Assuming the proportion of responders at Week 52 in the OLE study is 60%, it is estimated that approximately 360 patients will be randomized into this study.

With 360 patients, the study will have at least 90% power to detect a difference of 20% or greater between relugolix Group A and placebo Group B for the primary endpoint. The following assumptions are used to determine the sample size for this study:

- 2-sided type I error rate: 0.05
- Randomization: 1:1
- Responder rate for placebo Group B: 40%
- Responder rate for Group A: 60%
- Dropout rate: 20%

9.3.2. Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be assessed during the randomized treatment period or retreatment period:

- Proportion of women who maintain a menstrual blood loss volume of < 80 mL at Week 104 (52 weeks of the randomized treatment period) as measured by the alkaline hematin method;
- Change from Week 52/Baseline to Week 76/Week 104 in menstrual blood volume (during the randomized treatment period);
- Percentage change from Week 52/Baseline to Week 76 / Week 104 (during the randomized treatment period);
- Proportion of patients who responded (menstrual blood loss volume of < 80 mL) to retreatment with relugolix 40 mg and E2/NETA during the retreatment period among placebo patients whose menstrual blood volume had returned to ≥ 80 mL during the 52-week randomized treatment period;

The following secondary endpoints will be assessed at Week 76 and at Week 104 during the randomized treatment period:

- Proportion of women achieving or maintaining amenorrhea;
- Proportion of women whose menses has resumed (among those who were amenorrhoeic at Week 52/Baseline);
- Time to resumption of menses;
- Proportion of women with menstrual blood volume ≥ 80 mL at any time point during the 52-week randomized treatment period;
- Time to resumption of menstrual blood volume ≥ 80 mL;
- Change from Week 52/Baseline in hemoglobin;
- Change from Week 52/Baseline in SF-36 domain and summary component scores;
- Change from Week 52/Baseline in PGA for function and symptoms scores;
- Change from Week 52/Baseline in the WPAI-UF scores;
- Change from Week 52/Baseline in the UFS-QoL Symptom Severity scale and subscales as well as total scores.

9.3.2.1. Secondary Efficacy Endpoint Analyses

During Randomized Treatment Period

For endpoints evaluating the change from Baseline, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, randomization stratification factors, and treatment by visit interaction included as fixed effects and Week 52/Baseline value included as a covariate. The dependent variable (change from Baseline) for each patient at each visit will be calculated based on visit windows specified in the final Statistical Analysis Plan. In addition, descriptive statistics will be provided by treatment group and by visit.

Change from baseline endpoints will be analyzed censoring the values at the time of retreatment with relugolix with E2/NETA. Details will be specified in the SAP.

For endpoints evaluating proportions, treatment comparisons will be performed using a stratified Cochran-Mantel-Haenszel test as appropriate.

Baseline menstrual blood loss is defined as total menstrual blood loss obtained from the Week 52/Baseline visit prior to the date of the first dose of study drug in this Randomized Withdrawal study as assessed by the alkaline hematin method. The menstrual blood loss during the last on-treatment cycle (Week 104) is the total menstrual blood loss during the last month (up to the last 35 days) on-treatment as assessed by the alkaline hematin method.

For time-to-event endpoints (time to achieving or maintaining a menstrual blood loss volume of < 80 mL 24 weeks after randomization, time to resuming menses, time to resumption of menstrual blood volume ≥ 80 mL), time-to-event will be defined as weeks from randomization of the Randomized Withdrawal study to first occurrence of the event. Patients without an event will be censored at last assessment date prior to the end of study. Kaplan-Meier methods will be used to describe the time to event distributions for each study treatment arm.

For binary endpoints, the point estimate and 2-sided 95% CI for the proportion will be provided by study treatment group.

During Retreatment Period

For placebo patients whose menstrual blood volume had returned to ≥ 80 mL during the 52-week randomized treatment period and received retreatment:

- the proportion of patients who responded to the retreatment (MBL < 80mL) will be estimated along with corresponding 95% CIs at the end of retreatment period
- mean change and mean % change in menstrual blood volume from retreatment to end of retreatment period.

Details on the endpoint analyses including derivations, handling of missing data, and statistical methods will be provided in the SAP.

9.4. Pharmacodynamic Analyses

Pharmacodynamic estradiol concentration data will be listed and summarized by treatment arm and visit.

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECGs, and results of measurements of bone mineral density by DXA.

The treatment-emergent period will be defined as the period of time from the first dose date of extension study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. 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 study Baseline versus post-baseline results. All data will be listed and summarized by visit. The change from study Baseline to each post-baseline study visit will be presented by study treatment group for each laboratory test.

For vital signs parameters, including temperature, all data will be listed and summarized by visit. The change from study Baseline to each post-baseline study visit will be presented by study treatment group for each parameter.

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses.

The incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by the study treatment arm.

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

All BMD data will be listed and summarized by visit. The change, percent change from study Week 52/Baseline to Weeks 76 and 104 and associated 95% CIs will be presented by the study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 3%, 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the study treatment group.

Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a US investigational new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This

requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for 1 year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient.

10.1.4. Confidentiality

The investigator must assure that patient's anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the sponsor, IRB or IEC, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, protocol, eCRFs and other study forms, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

1) Investigator's study file. The investigator's study file will contain the Investigator's Brochure, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (e.g., history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;
   - Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
   - Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
   - Concomitant medication (including start and end date); and
   - Date of study completion and reason for early discontinuation, if applicable.

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the Investigator's Brochure, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and

signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

Should the investigator wish to assign the study records to another party or move them to another location, the sponsor must be notified in advance.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

10.1.7. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the investigator or sub-investigator (as appropriate) listed on Form FDA 1572 and/or other appropriate local health authority documents within a reasonable time period after data collection. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (i.e., pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

10.1.9. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

10.1.10. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to patients, may be made only by the sponsor. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

When a protocol amendment substantially alters the study design or the potential risks or burden to patients, the informed consent form will be amended and approved by the IRB or IEC, and all patients on treatment will again provide informed consent.

10.2.2. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies). The sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins. Results will be posted as required.

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The study monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

10.3.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of the sponsor may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor's medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10.3.3. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies) and IRBs/IECs. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the study participants interests.

10.3.4. Publications

After conclusion of the study and without prior written approval from the sponsor, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1.4).

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 90 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 120 days in order to obtain patent protection if deemed necessary.

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APPENDICES

Appendix 1. Health Survey Standard (SF-36v2®)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the past 4 weeks, how much did pain interfere with your norma work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 2. Patient Global Assessment (PGA) for Function and Symptoms

Patient Global Assessment (for function)

How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. No limitation at all
2. Mild limitation
3. Moderate limitation
4. Quite a bit of limitation
5. Extreme limitation

Patient Global Assessment (for symptoms)

How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks?

1. Not severe
2. Mildly severe
3. Moderately severe
4. Very severe
5. Extremely severe

Appendix 3. Work Productivity Activity Impairment -Uterine Fibroids (WPAI-UF)

Work Productivity and Activity Impairment Questionnaire:
Uterine Fibroids V2.0 (WPAI:UF)

The following questions ask about the effect of uterine fibroid symptoms on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO _____ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your uterine fibroid symptoms? *Include hours you missed on sick days, times you went in late, left early, etc., because of your uterine fibroid symptoms. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____ HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS *(If "0", skip to question 6.)*

English for USA – WPAI:UF V2.0 – 10/FEB/2016

5. During the past seven days, how much did your uterine fibroid symptoms affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If uterine fibroid symptoms affected your work only a little, choose a low number. Choose a high number if uterine fibroid symptoms affected your work a great deal.

Consider only how much uterine fibroid symptoms affected productivity while you were working.

Uterine fibroid symptoms had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Uterine fibroid symptoms completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your uterine fibroid symptoms affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If uterine fibroid symptoms affected your activities only a little, choose a low number. Choose a high number if uterine fibroid symptoms affected your activities a great deal.

Consider only how much uterine fibroid symptoms affected your ability to do your regular daily activities, other than work at a job.

Uterine fibroid symptoms had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Uterine fibroid symptoms completely prevented me from doing my daily activities

CIRCLE A NUMBER

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993 Nov;4(5):353-65.

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

Pt. Initials: _____ **Pt. ID:** _____

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐	☐	☐	☐	☐
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐	☐	☐ 3	☐	☐
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐	☐	☐	☐	☐
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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The following questions ask about your feelings and experiences regarding the impact of uterine fibroid symptoms on your life. Please consider each question as it relates to your experiences with uterine fibroids during the previous 3 months.

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If the question does not apply to you, please check "none of the time" as your option.

During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Made you feel anxious about the unpredictable onset or duration of your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Made you anxious about traveling?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Interfered with your physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. Caused you to feel tired or worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. Made you decrease the amount of time you spent on exercise or other physical activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Made you feel as if you are not in control of your life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. Made you concerned about soiling underclothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. Made you feel less productive?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
17. Caused you to feel drowsy or sleepy during the day?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18. Made you feel self-conscious of weight gain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19. Made you feel that it was difficult to carry out your usual activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20. Interfered with your social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21. Made you feel conscious about the size and appearance of your stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22. Made you concerned about soiling bed linen?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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During the previous 3 months, how often have your symptoms related to uterine fibroids...	None of the time	A little of the time	Some of the time	Most of the time	All of the time
23. Made you feel sad, discouraged, or hopeless?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24. Made you feel down hearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25. Made you feel wiped out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26. Caused you to be concerned or worried about your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27. Caused you to plan activities more carefully?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
29. Caused you embarrassment?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30. Made you feel uncertain about your future?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31. Made you feel irritable?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32. Made you concerned about soiling outer clothes?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33. Affected the size of clothing you wear during your periods?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34. Made you feel that you are not in control of your health?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35. Made you feel weak as if energy was drained from your body?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36. Diminished your sexual desire?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
37. Caused you to avoid sexual relations?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Appendix 5. Assessment of Abnormal Liver Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with estradiol/norethindrone acetate or placebo) should be withheld for any liver test abnormality listed in Section 7.5.1, pending investigation of alternative causes of liver injury. Follow-up should continue until the liver test abnormalities resolve to baseline.

Monitor liver tests per the applicable schedule in Appendix Table 1, and per the investigations in Appendix Table 2. If close monitoring is not possible, study drug should be withheld even if the results do not meet the criteria for withholding in Section 7.5.1.

The medical monitor should be contacted for questions regarding adequate follow-up tests and frequency of follow-up tests for a patient.

Appendix Table 1 Monitoring[a] of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (AST, ALT, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If AST or ALT ≥ 3 × ULN **and** total bilirubin > 2 × ULN **or** INR > 1.5	Every 24 hours until laboratory abnormalities improve
If ALT or AST ≥ 3 × ULN and total bilirubin and INR are normal	Every 48 to 72 hours until laboratory abnormalities improve
If the liver test abnormalities improve AND the patient is asymptomatic	Frequency may decrease

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; ULN, upper limit of normal

a. Review frequency of monitoring with medical monitor for an individual patient, in case of questions.

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination: • Detailed history of symptoms (e.g., right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (e.g., travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents; • Prior and concurrent use of alcohol, recreational drugs, and special diets; • Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms; • Physical examination.
Recommended tests: Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist. • Repeat liver tests as per Appendix Table 1; • Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests; • CBC with differential to assess for eosinophilia; • Serum acetaminophen (paracetamol) concentration; • Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus; • Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc; • Serology for celiac disease; • Appropriate liver imaging; • Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

a. If the first follow-up testing does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

AMENDMENT 1: SUMMARY OF CHANGES

The MVT-601-035 protocol has been amended as described in the table below. The primary purpose of the amendment is to provide clarification on the maintenance of blinding during pharmacodynamic testing and reporting of estradiol and FSH concentrations to the sponsor.

A detailed list of changes is described below, where deleted text is indicated by ~~strikethrough~~ and new text is indicated with **bold** formatting. Note that the correction of typos, minor clarifications, and minor wording changes to improve readability, understanding, and consistency may not be included in this table.

Section Item	Original	Amendment 1	Rationale
Section 1.1 Schedule of Activities Table 1-1 footnote l	Specimen for FSH will be collected ~~and stored until the study is unblinded. The assay for FSH will be performed after unblinding on amenorrhoeic patients who were assigned to placebo.~~.	Specimen for FSH will be **collected on patients who have been amenorrhoeic (i.e., those who have not required the use of any feminine products) since randomization.**	Clarification on FSH sample collection.
Section 5.7 Blinding	During the double-blind Randomized Treatment and through the Safety Follow-up period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes.	During the double-blind Randomized Treatment and through the Safety Follow-up period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes. **The blind will be maintained during assessment of pharmacodynamic testing. Estradiol and FSH concentrations will be reported to the sponsor only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.**	Language updated to clarify that blinding will be maintained during pharmacodynamic testing.
Section 6.5.2.4 Clinical Laboratory Samples	To maintain blinding, concentrations of ~~estradiol~~ hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding. ~~Specimens for FSH will be collected and stored until the study is unblinded. The assay for FSH will be performed after unblinding on amenorrhoeic patients who were assigned to placebo.~~	To maintain blinding, concentrations of hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.	Language updated to clarify that blinding will be maintained during pharmacodynamic testing.