16.1.1. Protocol and Protocol Amendments

- Amendment 1 (18 Oct 2018)
- Original Protocol (08 Aug 2017)

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3003
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	Eudra CT # 2017-003310-74 IND # 131161
Version and Effective Date:	Original: 08AUG-2017 Amendment 1: 18 October 2018

SPONSOR SIGNATURE PAGE

LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number: MVT-601-3003 Amendment 1

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

PPD

PPD PPD

22 Oct 2018
Date

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22 Oct 2018
Date

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22 Oct 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
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dihyroepiandrosterone
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
ICH	International Council on Harmonisation
IEC	institutional ethics committee
INR	international normalized ratio
IRB	institutional review board
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menorrhagia Impact Questionnaire
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
RBC	red blood cell
SAP	statistical analysis plan
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
US	United States
WBC	white blood cells

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3003
Location	Multinational, including North and South America, Europe, and South Africa
Study Centers	Approximately 240 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 600
Study Objectives	In women with heavy menstrual bleeding associated with uterine fibroids, the study objectives are as follows: <u>Primary Efficacy Objective</u> • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on heavy menstrual bleeding associated with uterine fibroids <u>Secondary Efficacy Objectives</u> • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on the following: o Achievement/maintenance of amenorrhea; o Hemoglobin; o Changes in symptom severity and quality of life related to uterine fibroids as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL); o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Uterine volume; o Uterine fibroid volume.

	Safety Objectives • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including: o Adverse events; o Changes in bone mineral density. Pharmacodynamic Objective • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on estradiol. Exploratory Objective • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002).

Study Design

The LIBERTY EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety extension study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for 28 weeks. Approximately 600 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) with relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Screening and baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study), which coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/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 (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3003 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. The administration of the first dose of study drug for MVT-601-3003 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for

28 weeks. Patients will complete daily paper diaries to record menstrual bleeding and feminine product use.

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA). Quality of life questionnaires will be completed according to the Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, and transvaginal ultrasound.

At the Week 52 visit or at an Early Termination visit occurring on or after Week 36, patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months. If Early Termination occurs prior to Week 36, follow-up bone densitometry will be performed according to the requirements of the parent study.

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, 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 apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3001 or MVT-601-3002;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-3003;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study may be done under the informed consent for the parent study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including during the Safety Follow-Up period;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;

5. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label 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 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the Week 24/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 (eg, 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 (MVT-601-3001 or MVT-601-3002);
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 (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
3. 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 parent study Week 24 DXA assessment of bone mineral density;
4. Anticipated to use any prohibited medications as detailed in Section 5.9.1;
5. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or 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. History of porphyria;
6. Has current active liver disease from any cause;

7. Has a systemic autoimmune disease (eg, 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; 8. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or any subsequent visit in one of the parent studies (MVT-601-3001 or MVT-601-3002): 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); 9. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug; 10. Has a decline in presenting visual acuity score as defined below (unless explained by refractive error or approved by the Sponsor): a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; OR b. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit; Note: visual acuity score must have been obtained with corrective lenses, if applicable; 11. 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. 12. Met a withdrawal criterion in the parent study (MVT-601-3001 or MVT-601-3002).	
Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 28 weeks (Open-Label Treatment period).
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for the extension study for all change from baseline-related endpoints. The menstrual blood loss during the screening period of the parent study will establish the patient's baseline for both the parent study and the extension study.

	Primary Efficacy Endpoint • Proportion of women who achieve or maintain a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline to the last 35 days of treatment, as measured by the alkaline hematin method. Secondary Efficacy Endpoints • Time to achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from parent study Baseline to Week 52 in menstrual blood loss; • Proportion of women who achieve or maintain amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve an increase of ≥ 1 g/dL from parent study Baseline at Week 52; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve a normal hemoglobin at Week 52; • Change from parent study Baseline to Week 52 in hemoglobin; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score; • Change from parent study Baseline to Week 52 in the MIQ score for physical activities; • Change from parent study Baseline to Week 52 in the MIQ score for social and leisure activities; • Change from parent study Baseline to Week 52 in uterine volume; • Change from parent study Baseline to Week 52 in uterine fibroid volume. Safety Endpoints • Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. Pharmacodynamic Endpoint • Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol. Exploratory Endpoint • Change from parent study Baseline to Week 52 in the EQ-5D-5L.
Statistical Methods Efficacy and safety data will be analyzed using descriptive statistics by the originally randomized treatment groups. There will be no between-treatment group comparisons for the extension study data. Efficacy Efficacy data will be summarized by the original randomized treatment group assigned in the parent study (ie, Groups A, B, and C) for the Intent-to-Treat Population. The analyses methods for efficacy endpoints are similar to those used for the parent studies, unless otherwise specified in the statistical analysis plan (SAP).	

The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoint (responder rate defined as proportion of women who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline in menstrual blood loss volume over the last 35 days of treatment) will be calculated.

The methods for analyzing the additional efficacy endpoints are described in the SAP.

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, and transvaginal ultrasound. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52).

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 parent study 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 24/Baseline, Week 36, and Week 52/Early Termination visits. The absolute, change, and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change at Week 52 from parent study Baseline in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3001 or MVT-601-3002) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the relugolix add-back treatment arm will be considered to have successfully prevented bone mineral density loss.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3001 or MVT-601-3002) and who are eligible and willing to participate in the extension study. It is estimated that approximately 600 patients (75% of the total of 780 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1: Schedule of Activities for Study MVT-601-3003

PERIOD	**OPEN-LABEL TREATMENT**									**SAFETY FOLLOW-UP**
VISIT NAME (Timing is relative to MVT-601-3001/-3002)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 – 10 to + 20**	**± 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
Vital Signs (BP, HR, Temperature)	X[g]	X	X	X	X	X	X	X	X[h]	X
Weight	X[g]			X				X	X[h]	
Complete Physical Examination	X[g]							X		
Visual Acuity[i]	X[g]									
Signs and Symptoms-Directed Physical Examination[j]		X	X	X	X	X	X		X[h]	X
12-Lead ECG[k]	X[g]							X	X[h]	
Clinical Laboratory Tests[l]	X[g,m]	X	X	X	X	X	X	X[m]	X[h]	X
Pharmacodynamics Sample[n]	X[g,m]							X[m]	X[h,m]	
Urinalysis	X[g]							X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X[h]	X

PERIOD	**OPEN-LABEL TREATMENT**									**SAFETY FOLLOW-UP**
VISIT NAME (Timing is relative to MVT-601-3001/-3002)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 – 10 to + 20**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**	**-**	**- 3 to + 18**
Transvaginal Ultrasound[o]	X[g]							X[p]	X[h]	
Bone Densitometry[q]	X[g]			X				X[p,r]	X[h]	
Endometrial Biopsy	X[g,s]							X[p]	X[h]	
Dispense Study Treatment	X	X	X	X	X	X	X		X[h]	
Patient Paper Diary[t]	X	X	X	X	X	X	X	X	X	
Dispense Feminine Products	X	X	X	X	X	X	X		X[h]	
Feminine Product Collection and Venous Blood Sample[u]	X[g]	X	X	X	X	X	X	X	X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic[v]	X[w]							X	X[h]	
Daily Self-Administration of Study Treatment[v]		X								
MIQ[x]	X[g]	X	X	X	X	X	X	X	X[h]	X
UFS-QoL Questionnaire[x]	X[g]			X				X	X[h]	
EQ-5D-5L Questionnaire[x]	X[g]							X	X[h]	
Adverse Event Collection[y]	X[z]	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery										X[aa]

BP, blood pressure; ECG, electrocardiogram; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; HR, heart rate; MIQ, Menorrhagia Impact Questionnaire; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life

[a] The week 52 visit must occur on or after the 1-year anniversary of Study Day 1 in the parent study. The timing of the visit should also be at least 28 weeks (± 10 days) from the actual date of the Week 24/Baseline visit.

[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 Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit.

[d] May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3003 is defined by administration of the first dose of MVT-601-3003 study drug.

[e] Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3003 should be reported as concomitant medications in the parent study (MVT-601-3001 or MVT-601-3002). Concomitant medications initiated during the MVT-601-3001 or MVT-60-3002 studies and ongoing at the time of the first dose in Study MVT-601-3003 will be recorded in the electronic case report form.

[f] Concomitant medications are recorded both for the parent study and for MVT-601-3003 at the Week 24/Baseline visit. (See footnote c for further details).

[g] This is a parent study (MVT-601-3001 or MVT-601-3002) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3003 and is covered under the informed consent for the parent study.

[h] The indicated procedure may be performed at the Unscheduled visit based on the purpose of the visit (eg, follow-up for an adverse event or abnormal laboratory test).

[i] See parent study protocols (MVT-601-3001 or MVT-601-3002) for instructions on testing visual acuity.

[j] The exam may include a gynecologic examination, if indicated based on signs and symptoms.

[k] The 12-lead ECGs will be submitted for central reading.

[l] Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. At the Week 24/Baseline visit and Week 52 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.

[m] Samples should be obtained in a fasted state (at least 8 hours). Water is allowed during the fasting period.

[n] Pharmacodynamic samples: For Week 24/Baseline samples, see the parent protocol (MVT-601-3001 or MVT-601-3002). At Week 52/Early Termination, collect samples for analysis of estradiol concentrations only. On days when pharmacodynamic samples are collected, administer the study treatment after the pharmacodynamic sample collections are completed.

[o] Transvaginal ultrasound, with or without transabdominal ultrasound and with or without saline or gel contrast, is performed to determine uterine and myoma volumes and endometrial thickness 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. Note: Transvaginal ultrasound is required. 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.

[p] This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.

[q] Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading.

[r] At the Week 52 visit or at an Early Termination visit occurring on or after Week 36, patients with a bone mineral density loss of > 3 relative to the 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 (eg, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. If Early Termination occurs prior to Week 36, follow-up bone densitometry will be performed according to the requirements of the parent study. The follow-up bone densitometry will be submitted for central reading.

[s] Endometrial biopsies are to be performed per instructions in the parent study. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3001 (see MVT-601-3001 protocol for details) and in some patients who participated in MVT-601-3002 (see MVT-601-3002 protocol for details).

[t] Patients enter diary information on menstruation status and feminine product use daily starting on the day of the Week 24/Baseline Visit.

[u] A venous blood sample (for hemoglobin) must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment. The site must document the start and stop dates of the patient's menses corresponding to the collected feminine products.

[v] Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. The last dose of study drug will be taken in the clinic during the Week 52/Early Termination visit.

[w] Pregnancy test must be negative before the study drug dose is administered.

[x] The patient will enter her response(s) into an electronic tablet device at the site.

[y] Collect adverse events from the time that the first dose of study drug for MVT-601-3003 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3003 should be reported as an adverse event in the parent study (MVT-601-3001 or MVT-601-3002). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3003, please see the Study Reference Manual for instructions for recording the follow-up status.

[z] Adverse events are collected for both the parent study and for MVT-601-3003 at the Week 24/Baseline visit (see footnote v for further details).

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

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 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. 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 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, and more than 200,000 hysterectomies are 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 medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

Summaries of nonclinical toxicology and previous human experience with relugolix, including results of phase 1 and phase 2 studies in women with uterine fibroids or endometriosis and in men with prostate cancer, are provided in the current relugolix investigator brochure, along with a full discussion of the safety profile of relugolix.

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate 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 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 the human GnRH receptors present on the 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 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 extension study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including 24 weeks of treatment during the parent study) of relugolix co-administered with low-dose estradiol and norethindrone acetate.

Descriptive assessments of efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) on the extension study population, defined as patients who enrolled in MVT-601-3003 (ie, who received at least 1 dose of study drug in the extension study), for the following parent study treatment groups:

- Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study;
- Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study;
- Parent Study Group C: Randomized to placebo in the parent study.

The parent study Baseline will be used as the reference point for the extension study for all change from baseline-related endpoints. The menstrual blood loss during the screening period of the parent study will establish the patient's baseline for both the parent study and the extension study.

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

Objective(s)	Endpoint(s)
Symptom and Health-Related Quality of Life (UFS-QoL); o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Uterine volume; o Uterine fibroid volume.	≥ 1 g/dL from parent study Baseline at Week 52; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve a normal hemoglobin at Week 52; • Change from parent study Baseline to Week 52 in hemoglobin; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score; • Change from parent study Baseline to Week 52 in the MIQ score for physical activities; • Change from parent study Baseline to Week 52 in the MIQ score for social and leisure activities; • Change from parent study Baseline to Week 52 in uterine volume; • Change from parent study Baseline to Week 52 in uterine fibroid volume.
<u>Safety</u>	
• To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including: o Adverse events; o Changes in bone mineral density.	• Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).
<u>Pharmacodynamic</u>	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on estradiol.	• Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol.

Objective(s)	Endpoint(s)
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002).	• Change from parent study Baseline to Week 52 in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The LIBERTY EXTENSION study (MVT-601-3003) is an international phase 3 open-label, single-arm, long-term efficacy and safety extension study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for 28 weeks. Approximately 600 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) with relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Screening and baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study), which coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/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 (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3003 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. The administration of the first dose of study drug for MVT-601-3003 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks. Patients will complete daily paper diaries to record menstrual bleeding and feminine product use.

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via DXA. Quality of life questionnaires will be completed according to the Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, and transvaginal ultrasound.

At the Week 52 visit or at an Early Termination visit occurring on or after Week 36, patients with a bone mineral density loss of > 3 relative to the 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 (eg, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. If Early Termination occurs prior to Week 36,

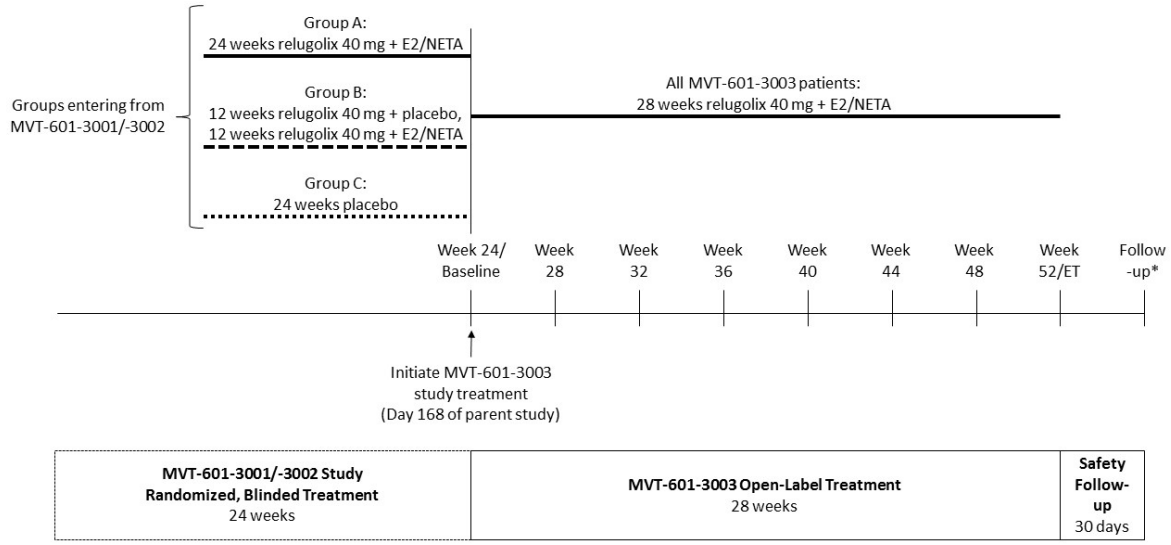
follow-up bone densitometry will be performed according to the requirements of the parent study. The follow-up bone densitometry will be submitted for central reading.

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, may be waived.

A schematic of the overall study design is provided Figure 1 .

Figure 1: MVT-601-3003 Study Schematic



E2/NETA = estradiol 1.0 mg / norethindrone acetate 0.5 mg
ET = Early Termination
*The Follow-up visit is scheduled ~30 days after the last dose of study drug.

4.2. Discussion of Study Design, Including Dosing

The LIBERTY EXTENSION study (MVT-601-3003) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3001 and MVT-601-3002) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This 28-week extension study provides additional efficacy and safety data up to 52 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objective of the study is to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks on reduction in heavy menstrual bleeding, the most

common and burdensome symptom of uterine fibroids. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation 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 most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 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 is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy 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 had 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 and, based on the DXA data from the phase 2 study, 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 to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 52 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 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 [Kliovance® SmPC, 2016]. 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 this 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 [Kliovance SmPC, 2016].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the 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 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 [Kliovance SmPC, 2016]) 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 study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3001 and MVT-601-3002) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose 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 a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 28 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3001 and MVT-601-3002). This study design will allow eligible patients with heavy menstrual bleeding associated with uterine fibroids, who were randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 600 women who have completed one of the parent studies (MVT-601-3001 or MVT-601-3002) to this extension study and meet all eligibility criteria for this study. Patients enrolled in the parent studies were premenopausal women with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

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 apply and have been met at the time of the Week 24/Baseline visit, unless otherwise specified:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3001 or MVT-601-3002;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-3003;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study may be done under the informed consent for the parent study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including during the Safety Follow-Up period;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label 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 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the Week 24/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 (eg, 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

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 (MVT-601-3001 or MVT-601-3002);
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 (eg, bilateral hip replacement, spinal hardware in the lumbar spine);

3. 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 parent study Week 24 DXA assessment of bone mineral density;
4. Anticipated to use any prohibited medications as detailed in Section 5.9.1;
5. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
    d. History of or 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. History of porphyria;
6. Has current active liver disease from any cause;
7. Has a systemic autoimmune disease (eg, 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;
8. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or any subsequent visit in one of the parent studies (MVT-601-3001 or MVT-601-3002):
    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);
9. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
10. Has a decline in presenting visual acuity score as defined below (unless explained by refractive error or approved by the Sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; OR
    b. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

Note: visual acuity score must have been obtained with corrective lenses, if applicable;

11. 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.
12. Met a withdrawal criterion in the parent study (MVT-601-3001 or MVT-601-3002).

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 parent study. This extension study is a single-arm study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).

4.5. Removal of Patients from Therapy

Completion of the Week 52 visit 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 52 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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 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%);
- 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 ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- 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 attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address 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, and 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 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure) at least 4 months prior to the Week 24/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 (eg, 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 those for whom one of the above methods do not 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 just 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

In this extension study, all patients will receive the following open-label oral study treatment:

- 28 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Each patient will be instructed to take one tablet and one capsule per day.

Table 2: Description of MVT-601-3003 Study Drugs

Name of Investigational Product	Relugolix	Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material
Dosage Form	Tablet	Capsule
Unit Dose Strength	40 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily/ 28 weeks	Oral once daily/ 28 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) and 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 and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

5.3. Randomization and Stratification

This extension study is a single-arm, open-label study, and thus, patients are not randomized or stratified upon enrollment in this study.

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state (other than water, tea, or coffee) 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 treatment should be taken as close as possible to the same time of morning each day.

On Week 24/Baseline and Week 52 clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).

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 by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started 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°C to 25°C with excursion to 15°C to 30°C 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.

Relugolix 40 mg will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate.

5.7. Blinding

Blinding is not applicable for this open-label extension study.

5.8. Study Drug Accountability and Treatment Compliance

Patients should bring all unused and used study drug 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 (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. 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 3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 3 are prohibited at any time during the study through the 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 3: Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zolendronic 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	
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	

Drug Class	Examples	Comments
Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only Nova Ring	
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 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	Study drug may be held for a period of up to 2 weeks with medical monitor approval if short-term treatment with one of these medications is required (eg, to treat an infection).
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] 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 allowed

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 24/Baseline visit to the Week 52/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 extension 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 a 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 24/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 Section 1.1). Study procedures are briefly described within Section 6.6. 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 Section 1.1). The study is divided into 2 periods: Open-Label Treatment period and Safety Follow-Up period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Open-Label Treatment Period (Week 24/Baseline to Week 52)

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3001 or MVT-601-3002 will serve as the Week 24/Baseline procedures for patients who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

Once eligibility is determined, all additional Week24/Baseline visit procedures described in the Schedule of Activities (see Section 1.1) that were not performed as part of the Week 24 visit of the parent study will be completed. These include the following:

- Informed consent;
- Record concomitant medications;
- Dispense study treatment;
- Dispense feminine products and paper diary with instructions to begin recording information daily;Take study drug dose in clinic; and
- Record adverse events, if any.

Patients will commence taking their open-label treatment once daily, beginning on the day of the Week 24/Baseline visit and continuing through the Week 52 visit. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, and 52.

At each post-Week24/Baseline visit, patients will return their feminine products for alkaline hematin testing. The paper diary will be reviewed at each visit. A venous blood sample (for hemoglobin) must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment. The site must document the start and stop dates of the patient's menses corresponding to the collected feminine products.

Safety monitoring including physical examination, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24/Baseline and

Week 52/Early Termination. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3001 (see MVT-601-3001 protocol for details) and in some patients who participated in MVT-601-3002 (see MVT-601-3002 protocol for details).

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 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

Refer to the Schedule of Activities (see Section 1.1) for information about study procedures during the Open-Label Treatment period.

6.3. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 52 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 52; however, for patients whose last dose of study drug is during Week 32 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), bone densitometry, and endometrial biopsy. These procedures may be performed at the investigator's discretion if they aid in follow-up of ongoing adverse events.

Patients (including those who complete the Week 52 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, for patients who enroll directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit may be waived.

The 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 (see Section 1.1) for individual study visit procedures during the Follow-up visit.

At an Early Termination visit occurring on or after Week 36, patients with a bone mineral density loss of > 3 relative to the 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 (eg, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. If Early Termination occurs prior to Week 36, follow-up bone densitometry will be performed according to the requirements of the parent study. The follow-up bone densitometry will be submitted for central reading.

6.4. Continuation into Randomized Withdrawal Study

Eligible patients may enter the 52-week randomized withdrawal study (MVT-601-035), which is conducted under a separate protocol. Patients will provide separate informed consent to participate for Study MVT-601-035, which will enroll patients who responded to study treatment

in this study and randomize them to receive relugolix 40 mg co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate, or placebo.

6.5. 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, 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 needed. See the Schedule of Activities (Section 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.

6.6. Study Procedures

6.6.1. Efficacy-Related Procedures

6.6.1.1. 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 collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. The site must document the start and stop dates of the patient's menses corresponding to the collected feminine products. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.6.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal ultrasound will be performed for all subjects. Once the transvaginal ultrasound is done, a transabdominal ultrasound, with or without saline or gel contrast, may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size. Transvaginal ultrasound, with or without transabdominal ultrasound, is performed to determine uterine and myoma volumes and endometrial thickness. 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; this single operator should be the same, if possible, as 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 x D2 x D3 x π / 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. The largest myoma among those measurable at the Screening 1 visit of the parent study (see the MVT-601-3001 or MVT-601-3002 protocol) will continue to be measured throughout the extension study.

Endometrial thickness will be locally assessed and recorded. Saline or gel contrast may be used to supplement sonographic assessment of the endometrium, as needed.

6.6.1.3. Endometrial Biopsy

Per the parent study MVT-601-3001 protocol, an endometrial biopsy is performed for all subjects at the Week 24 visit, whereas per the parent study MVT-601-3002 protocol, an endometrial biopsy is performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). If the required Week 24 biopsy is inadequate for diagnosis, it should be repeated, and a sample submitted to the central laboratory. If the second sample is inadequate, ensure an endometrial thickness has been reported from the Week 24 transvaginal ultrasound and contact the medical monitor to review the findings. Patients who have endometrial hyperplasia or endometrial carcinoma, will be withdrawn from study drug treatment and followed per instructions in the parent study protocol.

Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 and submitted to the central laboratory. If the Week 52 biopsy specimen is inadequate, the endometrial thickness reported at the Week 52 transvaginal ultrasound will be used to determine if further action is required:

- Endometrial thickness ≤ 5 mm – no further action required.
- Endometrial thickness > 5 mm at any location or any other endometrial abnormality – repeat endometrial sampling. Contact medical monitor if second specimen is inadequate for diagnosis.

Patients who decline endometrial sampling at Week 52 will not be prohibited from participating in the randomized withdrawal study.

Unscheduled endometrial biopsies may also be performed when medically indicated and as deemed necessary by the investigator. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy, unless urgently indicated. Additional consent is not required in this circumstance.

6.6.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum estradiol will be collected pre-dose at the visits indicated in the study Schedule of Activities (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory.

6.6.1.5. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 1). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the Open-Label Treatment period. Patients will complete the MIQ at each visit at the site before other study procedures, such as blood draws and physical examinations, are performed.

6.6.1.6. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 1). Patients will complete the UFS-QoL questionnaire at the site at the Week 24/Baseline visit, Week 36, and Week 52/Early Termination visit before other study procedures, such as blood draws and physical examinations, are performed.

6.6.1.7. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale is a standardized instrument for use as a measure of health outcomes (see Appendix 2). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D-5L questionnaire at the site at the Week 24/Baseline visit and the Week 52/Early Termination visit before other study procedures, such as blood draws and physical examinations, are performed.

6.6.1.8. Patient Diary

All women enrolled in the study will be provided with a patient paper diary, along with detailed instructions for its use. Patients will use the daily diary to record menstrual bleeding and use of feminine products. The diary will be reviewed by study staff at each visit.

6.6.2. Safety-Related Procedures

6.6.2.1. Weight

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

6.6.2.2. 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.

6.6.2.3. Physical and Gynecologic Examinations

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, 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.

6.6.2.4. 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 Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled 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 safety parameters will be provided to the site by the central laboratory. The samples collected for clinical laboratory tests are listed in Table 4 .

Table 4: Clinical Laboratory Tests

<table>
<tr><th>Chemistry</th><th>Hematology</th><th>Urinalysis</th></tr>
<tr><td rowspan="5">Potassium
Chloride
Bicarbonate
Blood Urea Nitrogen
Creatinine
Glucose
Calcium
Phosphate
Magnesium
Sodium
Albumin
Creatinine Kinase
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
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</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.

6.6.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at Week 24 visit in the parent study and at the Week 52/Early Termination 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.

6.6.2.6. 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 used at each site and operated in the same scan mode for all scans for an individual patient, and should be the same as used for the patient during the parent study (MVT-601-3001 or MVT-601-3002). 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 subject will be monitored by a central radiology laboratory over the course of the study.

Patients who experience a bone mineral density loss from the parent study Baseline of $\geq$ 7% at any of the anatomical sites assessed will be discontinued from the extension study. Patients should be assessed for secondary causes of bone loss if determined necessary by the investigator and followed up to resolution if bone mineral density loss is determined by the investigator to be related to study drug.

At Week 52 or an Early Termination visit occurring on or after Week 36, patients with a bone mineral density loss of > 3% at lumbar spine or total hip relative to parent study Baseline measurement will undergo another bone densitometry scan at 6 ($\pm$ 1) months and will be contacted to obtain information about medications and conditions (eg, pregnancy) that might

affect bone mineral density through the time of the follow-up bone densitometry. If Early Termination occurs prior to Week 36, follow-up bone densitometry will be performed according to the requirements of the parent study. The follow-up bone densitometry will be submitted for central reading.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the follow-up bone densitometry scan at 6 (± 1) months conducted under this protocol may be waived.

6.6.2.7. Status of Menstruation Recovery

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 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), ECGs, bone mineral density assessments, and clinical laboratory tests.

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 (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and
- An investigational abnormality (eg, 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 (eg, 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 (eg, 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:

1. Results in death;
2. 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.

3. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. 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 24/Baseline visit is not considered an adverse event.

4. 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 (eg, sprained ankle), which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect;
6. 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 or not 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 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 (Section 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 or not 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 5 should be used to determine the grade severity.

Table 5: 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 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 3.

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 24/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 (ie, 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:
   a. Hepatobiliary tract disease;
   b. Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);
   c. Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
   d. Alcoholic hepatitis;
   e. Nonalcoholic steatohepatitis;
   f. 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 QuintilesIMS Safety:

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 Africa: see region-specific phone numbers accompanying the Safety Report Form

The initial report should include:

- Study number (MVT-601-3003);
- 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 (ie, 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 or not 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.

A 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 this information, 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 6.6.2 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 (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, 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. Low-dose hormonal add-back therapy with estradiol and 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 brochure.

The risk assessment and mitigation strategy for this protocol are outlined in Table 6 .

Table 6: 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 low-dose estradiol and 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 24/Baseline, Week 36, and Week 52/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 24/Baseline and Week 52/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes 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 Open-Label 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 non-hormonal 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) Low-dose 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 malignances, 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 24/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 (eg, 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 (eg, 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.

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

9.1. Randomization Methods

This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for 28 weeks.

9.2. Analysis Populations

Efficacy data analyses will be performed on the Intent-to-Treat Population, defined as all patients who were randomized in a parent study and who have received any amount of study drug.

Safety data analyses will be performed on the Safety Population, defined as all patients who were randomized in a parent study and who have received any amount of study drug.

The analyses methods for safety and efficacy endpoints are similar to those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Estimation

Because this is an extension study, the sample size will be determined by the numbers of patients who have completed either parent study (MVT-601-3001 or MVT-601-3002) and who are eligible and willing to participate in this study. It is estimated that approximately 600 patients (75% of 780 patients who will be randomized in total into the parent studies) will participate in this extension study.

9.4. Efficacy Analyses

Efficacy endpoints will be summarized by the original treatment groups assigned in the parent study.

Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies.

- Proportion of women who achieve or maintain a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline to the last 35 days of treatment, as measured by the alkaline hematin method.
- Time to achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume as measured by the alkaline hematin method;

- Change from parent study Baseline to Week 52 in menstrual blood loss;
- Proportion of women who achieve or maintain amenorrhea over the last 35 days of treatment;
- Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve an increase of ≥ 1 g/dL from parent study Baseline at Week 52;
- Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve a normal hemoglobin at Week 52;
- Change from parent study Baseline to Week 52 in hemoglobin;
- Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity;
- Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score;
- Change from parent study Baseline to Week 52 in the MIQ score for physical activities;
- Change from parent study Baseline to Week 52 in the MIQ score for social and leisure activities;
- Change from parent study Baseline to Week 52 in uterine volume;
- Change from parent study Baseline to Week 52 in uterine fibroid volume.

The point estimate and 2-sided 95% confidence interval (CI) for the responder rate (defined as proportion of women who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from the parent study Baseline in menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method), will be calculated for each parent study treatment group.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug in the parent study as assessed by the alkaline hematin method. The menstrual blood loss during the last on-treatment cycle (Week 52) is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method.

Patients from Group C, who discontinue the extension study before Week 32 (28 days) will be considered non-responders.

For the endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume, time to event will be defined as weeks from randomization in the parent study to first occurrence of the event as assessed by the alkaline hematin method. 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 parent study treatment arm.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Uterine Fibroid Scale – Symptom Severity, Menorrhagia Impact Questionnaire Score, Numerical Rating

Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume to parent study Baseline.

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

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, and 12-lead ECGs.

The treatment-emergent period will be defined as the period of time from the first dose date of study drug in the parent study 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 parent study Baseline versus post-baseline results. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by parent 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 parent study Baseline to each post-baseline study visit will be presented by parent 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. ECGs will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic) mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for % change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group.

All data will be listed and summarized by visit. The change, percent change from parent study Baseline to Weeks 36 and 52 and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the parent 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. Pharmacodynamic Analyses

The change from the parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.

9.7. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed:

- Change from parent study Baseline to Week 52 in the European Quality of Life Five-Dimension Five-Level scale.

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 Council 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 patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, 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 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 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:
    a. Patient identification (name, date of birth, gender);
    b. Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
    c. Participation in the study (including study number);
    d. Study discussed and date of informed consent;
    e. Dates of all visits;
    f. Documentation that protocol-specific procedures were performed;
    g. Results of efficacy parameters, as required by the protocol;
    h. Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);

i. Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
j. Concomitant medication (including start and end date); and
k. 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 (ie, 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 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 (ie, 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. MENORRHAGIA IMPACT QUESTIONNAIRE

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

APPENDIX 2. 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?	☐	☐	☐	☐	☐
24. Made you feel down hearted and blue?	☐	☐	☐	☐	☐
25. Made you feel wiped out?	☐	☐	☐	☐	☐
26. Caused you to be concerned or worried about your health?	☐	☐	☐	☐	☐
27. Caused you to plan activities more carefully?	☐	☐	☐	☐	☐
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐	☐	☐	☐	☐
29. Caused you embarrassment?	☐	☐	☐	☐	☐
30. Made you feel uncertain about your future?	☐	☐	☐	☐	☐
31. Made you feel irritable?	☐	☐	☐	☐	☐
32. Made you concerned about soiling outer clothes?	☐	☐	☐	☐	☐
33. Affected the size of clothing you wear during your periods?	☐	☐	☐	☐	☐
34. Made you feel that you are not in control of your health?	☐	☐	☐	☐	☐
35. Made you feel weak as if energy was drained from your body?	☐	☐	☐	☐	☐
36. Diminished your sexual desire?	☐	☐	☐	☐	☐
37. Caused you to avoid sexual relations?	☐	☐	☐	☐	☐

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APPENDIX 3. EUROPEAN QUALITY OF LIFE FIVE-DIMENSION FIVE-LEVEL SCALE

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

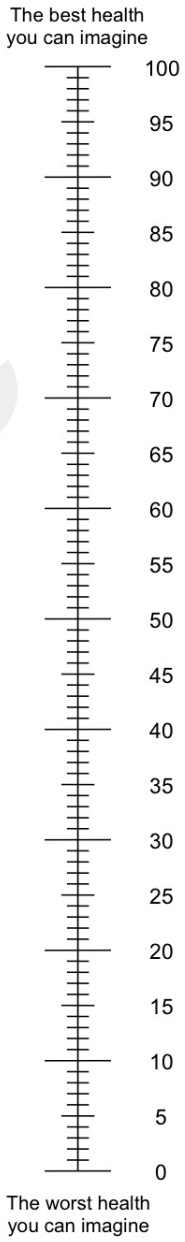
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 4. ASSESSMENT OF ABNORMAL LIVER TESTS

Study drug treatment (relugolix co-administered with low-dose estradiol and norethindrone acetate) 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 (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever); • Prior and concurrent disease or illnesses; • Exposure to environmental (eg, 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[a]; • 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:	LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3003
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	Eudra CT # 2017-003310-74 IND # 131161
Version and Effective Date:	Original Effective: 08-AUG-2017

SPONSOR SIGNATURE PAGE

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

Protocol Number: MVT-601-3003

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

PPD

PPD PPD

08 Aug 2017

Date

PPD

PPD PPD

8-Aug.-2017

Date

PPD

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8-Aug-2017

Date

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PPD PPD

8-Aug-2017

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
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dihyroepiandrosterone
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
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
MIQ	Menorrhagia Impact Questionnaire
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
RBC	red blood cell
SAP	statistical analysis plan
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
US	United States
WBC	white blood cells

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY EXTENSION: An International Phase 3 Open-Label, Single-Arm, Long-Term Efficacy and Safety Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3003
Location	Multinational, including North and South America, Europe, and South Africa
Study Centers	Approximately 240 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 600
Study Objectives	In women with heavy menstrual bleeding associated with uterine fibroids, the study objectives are as follows: <u>Primary Efficacy Objective</u> • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on heavy menstrual bleeding associated with uterine fibroids <u>Secondary Efficacy Objectives</u> • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on the following: o Achievement/maintenance of amenorrhea; o Hemoglobin; o Changes in symptom severity and quality of life related to uterine fibroids as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL); o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Uterine volume; o Uterine fibroid volume.

	Safety Objectives • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including: o Adverse events; o Changes in bone mineral density. Pharmacodynamic Objective • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on estradiol. Exploratory Objective • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002).

Study Design

The LIBERTY EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety extension study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 28 weeks. Approximately 600 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) with relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Screening and baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study), which coincides with the Week 24 visit from the parent study, and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/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 (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3003 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. The administration of the first dose of study drug for MVT-601-3003 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for

28 weeks.

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA). Quality of life questionnaires will be completed according to the Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, and transvaginal ultrasound.

Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months.

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, 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 apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3001 or MVT-601-3002;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-3003;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study may be done under the informed consent for the parent study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including during the Safety Follow-Up period;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label 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 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the Week 24/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 (eg, 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 (MVT-601-3001 or MVT-601-3002);
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 (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
3. 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 parent study Week 24 DXA assessment of bone mineral density;
4. Anticipated to use any prohibited medications as detailed in Section 5.9.1;
5. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or 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. History of porphyria;
6. Has current active liver disease from any cause;
7. Has a systemic autoimmune disease (eg, 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;
8. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or any subsequent visit in one of the parent studies (MVT-601-3001 or MVT-601-3002):
   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);
9. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
10. Has a decline in presenting visual acuity score as defined below (unless explained by refractive error or approved by the Sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; OR
    b. The presenting visual acuity score has decreased by 10 or more points at the

Week 24/Baseline visit relative to the parent study Baseline visit; Note: visual acuity score must have been obtained with corrective lenses, if applicable; 11. 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. 12. Met a withdrawal criterion in the parent study (MVT-601-3001 or MVT-601-3002).	
Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 28 weeks (Open-Label Treatment period).
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for the extension study for all change from baseline-related endpoints. The menstrual blood loss during the screening period of the parent study will establish the patient's baseline for both the parent study and the extension study. Primary Efficacy Endpoint • Proportion of women who achieve or maintain a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline to the last 35 days of treatment, as measured by the alkaline hematin method. Secondary Efficacy Endpoints • Time to achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from parent study Baseline to Week 52 in menstrual blood loss; • Proportion of women who achieve or maintain amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve an increase of ≥ 1 g/dL from parent study Baseline at Week 52; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve a normal hemoglobin at Week 52; • Change from parent study Baseline to Week 52 in hemoglobin;

	• Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score; • Change from parent study Baseline to Week 52 in the MIQ score for physical activities; • Change from parent study Baseline to Week 52 in the MIQ score for social and leisure activities; • Change from parent study Baseline to Week 52 in uterine volume; • Change from parent study Baseline to Week 52 in uterine fibroid volume. Safety Endpoints • Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. Pharmacodynamic Endpoint • Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol. Exploratory Endpoint • Change from parent study Baseline to Week 52 in the EQ-5D-5L.

Statistical Methods

Efficacy and safety data will be analyzed using descriptive statistics by the originally randomized treatment groups. There will be no between-treatment group comparisons for the extension study data.

Efficacy

Efficacy data will be summarized by the original randomized treatment group assigned in the parent study (ie, Groups A, B, and C) for the Intent-to-Treat Population. The analyses methods for efficacy endpoints are similar to those used for the parent studies, unless otherwise specified in the statistical analysis plan (SAP).

The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoint (responder rate defined as proportion of women who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline in menstrual blood loss volume over the last 35 days of treatment) will be calculated.

The methods for analyzing the additional efficacy endpoints are described in the SAP.

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, and transvaginal ultrasound. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52).

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 parent study 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 24/Baseline, Week 36, and Week 52/Early Termination visits. The absolute, change, and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change at Week 52 from parent study Baseline in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3001 or MVT-601-3002) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the relugolix add-back treatment arm will be considered to have successfully prevented bone mineral density loss.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3001 or MVT-601-3002) and who are eligible and willing to participate in the extension study. It is estimated that approximately 600 patients (75% of the total of 780 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3003

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3001/-3002)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 – 10 to + 20**	**± 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
Vital Signs (BP, HR, Temperature)	X[g]	X	X	X	X	X	X	X	X[h]	X
Weight	X[g]			X				X	X[h]	
Complete Physical Exam	X[g]							X		
Visual Acuity[i]	X[g]									
Signs and Symptoms-Directed Physical Exam[j]		X	X	X	X	X	X		X[h]	X
12-Lead ECG[k]	X[g]							X	X[h]	
Clinical Laboratory Tests[l]	X[g,m]	X	X	X	X	X	X	X[m]	X[h]	X
Pharmacodynamics Sample[n]	X[g,m]							X[m]	X[h,m]	
Urinalysis	X[g]							X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X[h]	X
Transvaginal Ultrasound[o]	X[g]							X[p]	X[h]	

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3001/-3002)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 – 10 to + 20**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**	**-**	**- 3 to + 18**
Bone Densitometry[q]	X[g]			X				X[p,r]	X[h]	
Endometrial Biopsy	X[g,s]								X[h]	
Dispense Study Treatment	X	X	X	X	X	X	X		X[h]	
Dispense Feminine Products	X	X	X	X	X	X	X		X[h]	
Feminine Product Collection and Venous Blood Sample[t]	X[g]	X	X	X	X	X	X	X	X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic[u]	X[v]							X	X[h]	
Daily Self-Administration of Study Treatment[u]		X								
MIQ[w]	X[g]	X	X	X	X	X	X	X	X[h]	X
UFS-QoL Questionnaire[w]	X[g]			X				X	X[h]	
EQ-5D-5L Questionnaire[w]	X[g]							X	X[h]	
Adverse Event Collection[x]	X[y]	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery										X[z]

Abbreviations: BP, blood pressure; ECG, electrocardiogram; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; HR, heart rate; MIQ, Menorrhagia Impact Questionnaire; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life

a. The Week 52 visit should occur on or after the 1-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 Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit.
d. May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3003 is defined by administration of the first dose of MVT-601-3003 study drug.
e. Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3003 should be reported as concomitant medications in the parent study (MVT-601-3001 or MVT-601-3002). If concomitant medication is ongoing at the time of the first dose of study drug for MVT-601-3003, please see the Study Reference Manual for instructions for recording the follow-up status.
f. Concomitant medications are recorded both for the parent study and for MVT-601-3003 at the Week 24/Baseline visit. (See footnote e for further details).
g. This is a parent study (MVT-601-3001 or MVT-601-3002) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3003 and is covered under the informed consent for the parent study.
h. The indicated procedure may be performed at the Unscheduled visit based on the purpose of the visit (eg, follow-up for an adverse event or abnormal laboratory test).
i. See parent study protocols (MVT-601-3001 or MVT-601-3002) for instructions on testing visual acuity.
j. The exam may include a gynecologic examination, if indicated based on signs and symptoms.
k. The 12-lead ECGs will be submitted for central reading.
l. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. At the Week 24/Baseline visit and Week 52 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.
m. Samples should be obtained in a fasted state (at least 8 hours). Water is allowed during the fasting period.
n. Pharmacodynamic samples: For Week 24/Baseline samples, see the parent protocol (MVT-601-3001 or MVT-601-3002). At Week 52/Early Termination, collect samples for analysis of estradiol concentrations only. On days when pharmacodynamic samples are collected, administer the study treatment after the pharmacodynamic sample collections are completed.
o. 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. Note: Transvaginal ultrasound is required. 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.
p. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.
q. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading.
r. Patients with a bone mineral density loss of > 3% at their Week 52/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 (eg, 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.
s. Endometrial biopsies are to be done per instructions in the parent study. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3001 (see MVT-601-3001 protocol for details) and in some patients who participated in MVT-601-3002 (see MVT-601-3002 protocol for details).
t. A venous blood sample (for hemoglobin) must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment. The site must document the start and stop dates of the patient's menses corresponding to the collected feminine products.

u. Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. The last dose of study drug will be taken in the clinic during the Week 52/Early Termination visit.
v. Pregnancy test must be negative before the study drug dose is administered.
w. The patient will enter her response(s) into an electronic tablet device at the site.
x. Collect adverse events from the time that the first dose of study drug for MVT-601-3003 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3003 should be reported as an adverse event in the parent study (MVT-601-3001 or MVT-601-3002). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3003, please see the Study Reference Manual for instructions for recording the follow-up status.
y. Adverse events are collected for both the parent study and for MVT-601-3003 at the Week 24/Baseline visit (see footnote x for further details).
z. Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted again by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.

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 25% of women of reproductive age. While the majority of uterine fibroids are asymptomatic, approximately 25% of women with fibroids develop symptoms requiring treatment. 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 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, and more than 200,000 hysterectomies are 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 medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

Summaries of nonclinical toxicology and previous human experience with relugolix, including results of phase 1 and phase 2 studies in women with uterine fibroids or endometriosis and in men with prostate cancer, are provided in the current relugolix investigator brochure, along with a full discussion of the safety profile of relugolix.

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate 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 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 the human GnRH receptors present on the 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 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 extension study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including 24 weeks of treatment during the parent study) of relugolix co-administered with low-dose estradiol and norethindrone acetate.

Descriptive assessments of efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) on the extension study population, defined as patients who enrolled in MVT-601-3003 (ie, who received at least 1 dose of study drug in the extension study), for the following parent study treatment groups:

- Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study;
- Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study;
- Parent Study Group C: Randomized to placebo in the parent study.

The parent study Baseline will be used as the reference point for the extension study for all change from baseline-related endpoints. The menstrual blood loss during the screening period of the parent study will establish the patient's baseline for both the parent study and the extension study.

Objective(s)	Endpoint(s)
Primary Efficacy	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on heavy menstrual bleeding associated with uterine fibroids.	• Proportion of women who achieve or maintain a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline to the last 35 days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on the following: o Achievement/maintenance of amenorrhea; o Hemoglobin; o Changes in symptom severity and quality of life related to uterine fibroids as measured by the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL); o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Uterine volume; o Uterine fibroid volume.	• Time to achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from parent study Baseline to Week 52 in menstrual blood loss; • Proportion of women who achieve or maintain amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve an increase of ≥ 1 g/dL from parent study Baseline at Week 52; • Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve a normal hemoglobin at Week 52; • Change from parent study Baseline to Week 52 in hemoglobin; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity; • Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score; • Change from parent study Baseline to Week 52 in the MIQ score for physical activities; • Change from parent study Baseline to Week 52 in the MIQ score for social and leisure activities; • Change from parent study Baseline to Week 52 in uterine volume; • Change from parent study Baseline to Week 52 in uterine fibroid volume.
Safety	
• To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including: o Adverse events; o Changes in bone mineral density.	• Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).

Objective(s)	Endpoint(s)
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), on estradiol.	• Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol.
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002).	• Change from parent study Baseline to Week 52 in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The LIBERTY EXTENSION study (MVT-601-3003) is an international phase 3 open-label, single-arm, long-term efficacy and safety extension study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3001 or MVT-601-3002). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 28 weeks. Approximately 600 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) with relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Screening and baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study), which coincides with the Week 24 visit from the parent study, and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/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 (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3003 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. The administration of the first dose of study drug for MVT-601-3003 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks.

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via DXA. Quality of life questionnaires will be completed according to the Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, and transvaginal ultrasound.

Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months.

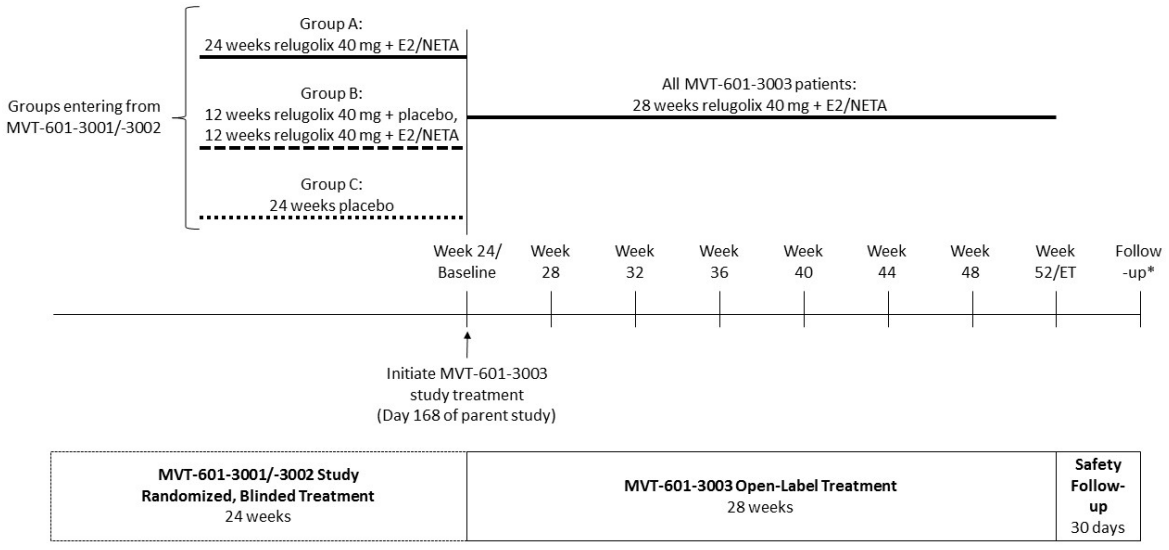
Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack

of resumption (eg, medical procedure or medications) will be contacted again by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, may be waived.

A schematic of the overall study design is provided as Figure 4-1.

Figure 4-1 MVT-601-3003 Study Schematic



E2/NETA = estradiol 1.0 mg / norethindrone acetate 0.5 mg
ET = Early Termination
*The Follow-up visit is scheduled ~30 days after the last dose of study drug.

4.2. Discussion of Study Design, Including Dosing

The LIBERTY EXTENSION study (MVT-601-3003) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3001 and MVT-601-3002) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This 28-week extension study provides additional efficacy and safety data up to 52 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objective of the study is to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks on reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3001 or MVT-601-3002), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation 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 most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 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 is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy 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 had 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 and, based on the DXA data from the phase 2 study, 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 to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 52 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 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, 2013]. 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 this 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, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the 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 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, 2013]) 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 study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3001 and MVT-601-3002) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose 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 a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate to decrease heavy menstrual bleeding associated with uterine fibroids and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 28 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3001 and MVT-601-3002). This study design will allow eligible patients with heavy menstrual bleeding associated with uterine fibroids, who were randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 600 women who have completed one of the parent studies (MVT-601-3001 or MVT-601-3002) to this extension study and meet all eligibility criteria for this study. Patients enrolled in the parent studies were premenopausal women with heavy menstrual bleeding associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

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 apply and have been met at the time of the Week 24/Baseline visit, unless otherwise specified:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3001 or MVT-601-3002;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures for MVT-601-3003;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study may be done under the informed consent for the parent study;
3. Is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the study period, including during the Safety Follow-Up period;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label 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 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the Week 24/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 (eg, 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

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 (MVT-601-3001 or MVT-601-3002);
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 (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
3. 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 parent study Week 24 DXA assessment of bone mineral density;
4. Anticipated to use any prohibited medications as detailed in Section 5.9.1;

5. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
    d. History of or 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. History of porphyria;
6. Has current active liver disease from any cause;
7. Has a systemic autoimmune disease (eg, 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;
8. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or any subsequent visit in one of the parent studies (MVT-601-3001 or MVT-601-3002):
    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);
9. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
10. Has a decline in presenting visual acuity score as defined below (unless explained by refractive error or approved by the Sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; OR
    b. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: visual acuity score must have been obtained with corrective lenses, if applicable;
11. 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.
12. Met a withdrawal criterion in the parent study (MVT-601-3001 or MVT-601-3002).

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 parent study. This extension study is a single-arm study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).

4.5. Removal of Patients from Therapy

Completion of the Week 52 visit 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 52 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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 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%);
- 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 ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- 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 attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address 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, and 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 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™) at least 4 months prior to the Week 24/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 (eg, 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 those for whom one of the above methods do not 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 just 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

In this extension study, all patients will receive the following open-label oral study treatment:

- 28 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Each patient will be instructed to take one tablet and one capsule per day.

Table 5-1 Description of MVT-601-3003 Study Drugs

Name of Investigational Product	Relugolix	Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material
Dosage Form	Tablet	Capsule
Unit Dose Strength	40 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily/ 28 weeks	Oral once daily/ 28 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) and 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 and norethindrone acetate 0.5 mg is encapsulated in a gelatin capsule with sufficient common back-fill material.

5.3. Randomization and Stratification

This extension study is a single-arm, open-label study, and thus, patients are not randomized or stratified upon enrollment in this study.

5.4. Directions for Administration

All study patients will take a study treatment of one tablet and one capsule once daily.

The study treatment should be taken in the fasted state (other than water, tea, or coffee) 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 treatment should be taken as close as possible to the same time of morning each day.

On Week 24/Baseline and Week 52 clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).

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 by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started 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°C to 25°C with excursion to 15°C to 30°C 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.

Relugolix 40 mg will be supplied to the study site in blister cards co-packaged with the estradiol/norethindrone acetate.

5.7. Blinding

Blinding is not applicable for this open-label extension study.

5.8. Study Drug Accountability and Treatment Compliance

Patients should bring all unused and used study drug 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 (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. 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 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 zolendronic 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	Note: All other anticonvulsants are allowed
Aromatase Inhibitors	anastrozole letrozole	
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	

Table 5-2 Prohibited Medications (Continued)

Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only Nova Ring	
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 copper	
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. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.

Table 5-2 Prohibited Medications (Continued)

P-glycoprotein Inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir	Study drug may be held for a period of up to 2 weeks with medical monitor approval if short-term treatment with one of these medications is required (eg, to treat an infection).
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycina captoprilb carvedilol clarithromycina conivaptan cyclosporinc diltiazem dronedarone erythromycina felodipined itraconazolee ketoconazolee lopinavir/ritonavirf quercetin quinidine ranolazine ticagrelortg erapamilv	Study drug may be held for a period of up to 2 weeks with medical monitor approval if short-term treatment with one of these medications is required (eg, to treat an infection).

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. Clopidogrel is allowed

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 24/Baseline visit to the Week 52/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 extension 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 a 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 24/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 Section 1.1). Study procedures are briefly described within 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 Section 1.1). The study is divided into 2 periods: Open-Label Treatment period and Safety Follow-Up period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Open-Label Treatment Period (Week 24/Baseline to Week 52)

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3001 or MVT-601-3002 will serve as the Week 24/Baseline procedures for patients who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

Once eligibility is determined, all additional Week24/Baseline visit procedures described in the Schedule of Activities (see Section 1.1) that were not performed as part of the Week 24 visit of the parent study will be completed. These include the following:

- Informed consent;
- Record concomitant medications;
- Dispense study treatment;
- Dispense feminine products;
- Take study drug dose in clinic; and
- Record adverse events, if any.

Patients will commence taking their open-label treatment once daily, beginning on the day of the Week 24/Baseline visit and continuing through the Week 52 visit. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, and 52.

At each post-Week24/Baseline visit, patients will return their feminine products for alkaline hematin testing. A venous blood sample (for hemoglobin) must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment. The site must document the start and stop dates of the patient's menses corresponding to the collected feminine products.

Safety monitoring including physical examination, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the

Week 24/Baseline, Week 36, and Week 52/Early Termination visits. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24/Baseline and Week 52/Early Termination. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3001 (see MVT-601-3001 protocol for details) and in some patients who participated in MVT-601-3002 (see MVT-601-3002 protocol for details).

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 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

Refer to the Schedule of Activities (see Section 1.1) for information about study procedures during the Open-Label Treatment period.

6.3. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 52 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 52; however, for patients whose last dose of study drug is during Week 32 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound) and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

Patients (including those who complete the Week 52 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, for patients who enroll directly into another relugolix clinical study upon completion of the Week 52 visit, then the Follow-up visit may be waived.

The 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 (see Section 1.1) for individual study visit procedures during the 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, 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 needed. See the Schedule of Activities (Section 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. 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 collected at each visit until the patient completes treatment or terminates participation from the study prior to completing treatment. The site must document the start and stop dates of the patient's menses corresponding to the collected feminine products. Each time the patient submits her feminine products from a menstrual cycle for analysis, a venous blood sample will be collected and sent to the laboratory. Details regarding materials, process, and requirements for the menstrual blood loss collection will be provided in the Study Reference Manual.

6.5.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal ultrasound will be performed for all subjects. Once the transvaginal ultrasound is done, a transabdominal ultrasound, with or without saline or gel contrast, may also be done if the uterus cannot be adequately imaged on transvaginal ultrasound; for example, due to enlarged size. Transvaginal ultrasound, with or without transabdominal ultrasound, is performed to determine uterine and myoma volumes. 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; this single operator should be the same, if possible, as 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 x D2 x D3 x π / 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. The largest myoma among those measurable at the Screening 1 visit of the parent study (see the MVT-601-3001 or MVT-601-3002 protocol) will continue to be measured throughout the extension study.

6.5.1.3. Endometrial Biopsy

Per the parent study MVT-601-3001 protocol, an endometrial biopsy is performed for all subjects at the Week 24 visit, whereas per the parent study MVT-601-3002 protocol, an endometrial biopsy is performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound).

Patients who have endometrial hyperplasia or endometrial carcinoma, will be withdrawn from study drug treatment and followed per instructions in the parent study protocol.

6.5.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum estradiol will be collected pre-dose at the visits indicated in the study Schedule of Activities (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory.

6.5.1.5. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire was designed to measure a women's self-assessment of menstrual blood loss and its impact on her social and leisure activities, physical activities, and ability to work (see Appendix 1). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the Open-Label Treatment period. Patients will complete the MIQ at each visit at the site before other study procedures, such as blood draws and physical examinations, are performed.

6.5.1.6. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related Quality of Life score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 2). Patients will complete the UFS-QoL questionnaire at the site at the Week 24/Baseline visit, Week 36, and Week 52/Early Termination visit before other study procedures, such as blood draws and physical examinations, are performed.

6.5.1.7. European Quality of Life Five-Dimension Five-Level Scale

The European Quality of Life Five-Dimension Five-Level Scale is a standardized instrument for use as a measure of health outcomes (see Appendix 3). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on 5-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D-5L questionnaire at the site at the Week 24/Baseline visit and the Week 52/Early Termination visit before other study procedures, such as blood draws and physical examinations, 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 head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, 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.

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 Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled 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 safety parameters 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

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Creatinine Kinase Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte Esterase Ketones Nitrite Specific Gravity Urine Microscopy (reflex testing based on abnormal urine analysis)
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones		
Estradiol		

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.

6.5.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at Week 24 visit in the parent study and at the Week 52/Early Termination 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.

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 used at each site and operated in the same scan mode for all scans for an individual patient, and should be the same as used for the patient during the parent study (MVT-601-3001 or MVT-601-3002). 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 subject will be monitored by a central radiology laboratory over the course of the study.

Patients who experience a bone mineral density loss from the parent study Baseline of ≥ 7% at any of the anatomical sites assessed will be discontinued from the extension study. Patients should be assessed for secondary causes of bone loss if determined necessary by the investigator and followed up to resolution if bone mineral density loss is determined by the investigator to be related to study drug.

Patients with a bone mineral density loss of > 3% at lumbar spine or total hip at their Week 52/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 (eg, 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.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, then the follow-up bone densitometry scan at 6 (± 1) months conducted under this protocol may be waived.

6.5.2.7. Status of Menstruation Recovery

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 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), ECGs, bone mineral density assessments, and clinical laboratory tests.

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 (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and
- An investigational abnormality (eg, 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 (eg, 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 (eg, 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 detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. 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 24/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 (eg, 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 or not 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 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 (Section 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:

a. **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).
b. **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.
c. **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 or not 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 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 4.

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 24/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 (ie, 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 (eg, 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 QuintilesIMS Safety:

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 Africa: see region-specific phone numbers accompanying the Safety Report Form

The initial report should include:

- Study number (MVT-601-3003);
- 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 (ie, 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 or not 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.

A 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 this information, 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 (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, 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. Low-dose hormonal add-back therapy with estradiol and 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 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 low-dose estradiol and 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 24/Baseline, Week 36, and Week 52/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 24/Baseline and Week 52/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes 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 Open-Label Treatment period will be reported within 24 hours of study personnel awareness.

Table 7-2 Protocol Risk Assessment and Mitigation Strategies (Continued)

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 non-hormonal 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) Low-dose 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 malignances, 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 24/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 (eg, 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 (eg, 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.

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

9.1. Randomization Methods

This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for 28 weeks.

9.2. Analysis Populations

Efficacy data analyses will be performed on the Intent-to-Treat Population, defined as all patients who were randomized in a parent study and who have received any amount of study drug.

Safety data analyses will be performed on the Safety Population, defined as all patients who were randomized in a parent study and who have received any amount of study drug.

The analyses methods for safety and efficacy endpoints are similar to those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Estimation

Because this is an extension study, the sample size will be determined by the numbers of patients who have completed either parent study (MVT-601-3001 or MVT-601-3002) and who are eligible and willing to participate in this study. It is estimated that approximately 600 patients (75% of 780 patients who will be randomized in total into the parent studies) will participate in this extension study.

9.4. Efficacy Analyses

Efficacy endpoints will be summarized by the original treatment groups assigned in the parent study.

Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies.

- Proportion of women who achieve or maintain a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline to the last 35 days of treatment, as measured by the alkaline hematin method.
- Time to achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume as measured by the alkaline hematin method;

- Change from parent study Baseline to Week 52 in menstrual blood loss;
- Proportion of women who achieve or maintain amenorrhea over the last 35 days of treatment;
- Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve an increase of ≥ 1 g/dL from parent study Baseline at Week 52;
- Proportion of women with a hemoglobin below the lower limit of normal at parent study Baseline who achieve a normal hemoglobin at Week 52;
- Change from parent study Baseline to Week 52 in hemoglobin;
- Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Symptom Severity;
- Change from parent study Baseline to Week 52 in the Uterine Fibroid Scale – Health-related Quality of Life subscales and total score;
- Change from parent study Baseline to Week 52 in the MIQ score for physical activities;
- Change from parent study Baseline to Week 52 in the MIQ score for social and leisure activities;
- Change from parent study Baseline to Week 52 in uterine volume;
- Change from parent study Baseline to Week 52 in uterine fibroid volume.

The point estimate and 2-sided 95% confidence interval (CI) for the responder rate (defined as proportion of women who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from the parent study Baseline in menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method), will be calculated for each parent study treatment group.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug in the parent study as assessed by the alkaline hematin method. The menstrual blood loss during the last on-treatment cycle (Week 52) is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method.

Patients from Group C, who discontinue the extension study before Week 32 (28 days) will be considered non-responders.

For the endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from parent study Baseline menstrual blood loss volume, time to event will be defined as weeks from randomization in the parent study to first occurrence of the event as assessed by the alkaline hematin method. 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 parent study treatment arm.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Uterine Fibroid Scale – Symptom Severity, Menorrhagia Impact Questionnaire Score, Numerical Rating

Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume to parent study Baseline.

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

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, and 12-lead ECGs.

The treatment-emergent period will be defined as the period of time from the first dose date of study drug in the parent study 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 parent study Baseline versus post-baseline results. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by parent 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 parent study Baseline to each post-baseline study visit will be presented by parent 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. ECGs will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic) mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for % change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group.

All data will be listed and summarized by visit. The change, percent change from parent study Baseline to Weeks 36 and 52 and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the parent 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. Pharmacodynamic Analyses

The change from the parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.

9.7. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed:

- Change from parent study Baseline to Week 52 in the European Quality of Life Five-Dimension Five-Level scale.

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 patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient number, date of birth, and an identification code (ie, 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 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 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, (eg, 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 (ie, 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 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 (ie, 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 Publically 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. Menorrhagia Impact Questionnaire

In addition to the MIQ items listed in the table, patients describe all activities that were limited by excessive bleeding (MIQ item 5).

MIQ concept	MIQ item	Response scale
Perception of amount of blood loss	MIQ 1 'During your most recent menstrual period, your blood loss was':	1. Light 2. Moderate 3. Heavy 4. Very Heavy
Limitations in work outside or inside the home	MIQ 2 'During your most recent menstrual period, how much did your bleeding limit you in your work outside or inside the home?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in physical activities	MIQ 3 'During your most recent menstrual period, how much did your bleeding limit you in your physical activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Limitations in social or leisure activities	MIQ 4 'During your most recent menstrual period, how much did your bleeding limit you in your social or leisure activities?'	1. Not At All 2. Slightly 3. Moderately 4. Quite A Bit 5. Extremely
Global assessment of change in blood loss	MIQ 6/6a/6b 'Compared to your previous menstrual period, would you say your blood loss during this period was':	0. About the same 1. Better (7-item scale): 1. Almost the same, hardly better at all 2. A little better 3. Somewhat better 4. An average amount better 5. A good deal better 6. A great deal better 7. A very great deal better 2. Worse (7-item scale): 1. Almost the same, hardly worse at all 2. A little worse 3. Somewhat worse 4. An average amount worse 5. A good deal worse 6. A great deal worse 7. A very great deal worse
Meaningfulness of perceived change in blood loss	MIQ 6c 'Was this a meaningful or important change for you?'	0. No 1. Yes

MIQ, Menorrhagia Impact Questionnaire.

Appendix 2. 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?	☐	☐	☐	☐	☐
24. Made you feel down hearted and blue?	☐	☐	☐	☐	☐
25. Made you feel wiped out?	☐	☐	☐	☐	☐
26. Caused you to be concerned or worried about your health?	☐	☐	☐	☐	☐
27. Caused you to plan activities more carefully?	☐	☐	☐	☐	☐
28. Made you feel inconvenienced about always carrying extra pads, tampons, and clothing to avoid accidents?	☐	☐	☐	☐	☐
29. Caused you embarrassment?	☐	☐	☐	☐	☐
30. Made you feel uncertain about your future?	☐	☐	☐	☐	☐
31. Made you feel irritable?	☐	☐	☐	☐	☐
32. Made you concerned about soiling outer clothes?	☐	☐	☐	☐	☐
33. Affected the size of clothing you wear during your periods?	☐	☐	☐	☐	☐
34. Made you feel that you are not in control of your health?	☐	☐	☐	☐	☐
35. Made you feel weak as if energy was drained from your body?	☐	☐	☐	☐	☐
36. Diminished your sexual desire?	☐	☐	☐	☐	☐
37. Caused you to avoid sexual relations?	☐	☐	☐	☐	☐

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Appendix 3. European Quality of Life Five-Dimension Five-Level Scale

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking	❑
I have slight problems walking	❑
I have moderate problems walking	❑
I have severe problems walking	❑
I am unable to walk	❑

SELF-CARE

I have no problems washing or dressing myself	❑
I have slight problems washing or dressing myself	❑
I have moderate problems washing or dressing myself	❑
I have severe problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities	❑
I have slight problems doing my usual activities	❑
I have moderate problems doing my usual activities	❑
I have severe problems doing my usual activities	❑
I am unable to do my usual activities	❑

PAIN / DISCOMFORT

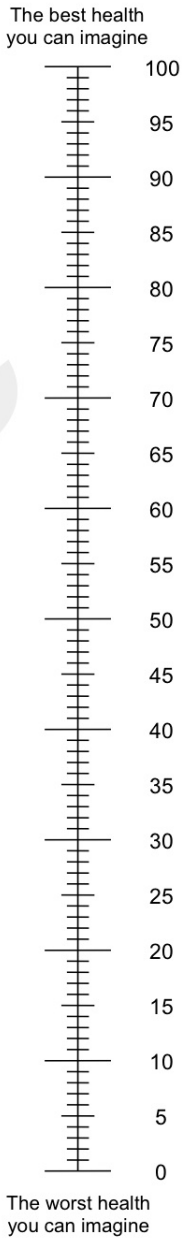
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 4. Assessment of Abnormal Liver Tests

Study drug treatment (blinded relugolix monotherapy or relugolix co-administered with low-dose estradiol and 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 4 Table 1, and per the investigations in Appendix 4 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 4 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 4 Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, 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 4 Table 1[a];
- 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.