Term	Explanation
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.

Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or ≥ 160 mL during 1 cycle during the screening period. During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24, followed by a repeat endometrial biopsy. Patients will have paired baseline and end-of-treatment endometrial biopsies, independent of ultrasound results. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X	X
12-Lead Electrocardiogram			X		X			X			X	X	X
Clinical Laboratory Tests[l]	X	X			X[i, j]	X	X	X	X	X	X[i, k]	X[l]	X
PK Sample[m]					X	X		X			X	X[l]	
PD Sample[n] and Administer Dose of Study Drug in Clinic	X				X	X	X	X	X	X	X		X
PGx Sample[o]					X								
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X		
Urinalysis	X				X								
Mammogram[p]			X										
Transvaginal or Transabdominal Ultrasound[q]			X								X		
Endometrial Biopsy[r]			X								X[s]		
Bone Densitometry[t]			X					X			X		
Randomization[u]					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X			
Dispense Study Treatment					X	X	X	X	X	X			
Patient eDiary[v]			X	X	X	X	X	X	X	X	X		
Feminine Product Collection and Venous Blood Sample[w]		X		X		X	X	X	X	X	X		
MIQ					X	X	X	X	X	X	X		
UFS-QoL					X			X			X		
EQ-5D					X						X		
Treatment Compliance						X	X	X	X	X	X	X	

Objective(s)	Endpoint(s)
	the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks.	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.

4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal and/or transabdominal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Samples will also be collected for PK assessment of relugolix, estradiol, and norethindrone, and for the pharmacodynamic assessment of LH, FSH, estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit to assess safety approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits and dispensation and collection of feminine products during this time are provided in Figure 4-2.

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 48 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 48 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, 1992; 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 has demonstrated that this dose of add-back therapy maintains serum estradiol in the 25-50 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 PK 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) 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 is not included as a control arm as 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

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities in the study synopsis (see Section 1.1). The study is divided into three periods: screening period, randomized treatment period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study; unscheduled visits may also occur as needed to evaluate patients).

6.2. Screening Period

Patients should have a diagnosis of uterine fibroids and a history of heavy menstrual bleeding with or without associated pain on a background of generally regular menses (ie, regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next menstrual period) as reported by the patient for at least 3 months prior to the Screening 1 visit.

The screening period consists of the Screening 1, 2, 3, and 4 visits.

See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening. The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

6.2.1. Screening 1 Visit

The Screening 1 visit will be conducted following the signing of the informed consent form and may occur at any time during the menstrual cycle. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications, study procedure-related adverse events and any serious adverse events. In addition, vital signs, height, weight, temperature, a complete physical examination, gynecology examination, ultrasound, endometrial biopsy, Papanicolaou test (if needed), clinical laboratory tests, urinalysis, and a urine pregnancy test will be done. Feminine products will be dispensed with instructions to collect and return all products used during the next menses. The paper diary will also be dispensed at this visit and should be completed daily starting with this visit. The bone mineral density scan and mammogram should be scheduled at this time (or within a few days of this visit). Bone densitometry should be scheduled to be prior to the Screening 3 visit and as early as feasible to ensure results are available prior to randomization.

The order of procedures should be as follows. Patients not meeting eligibility criteria after any procedure should not undergo subsequent procedures.

- Medical history and review of prior uterine imaging studies
- Review of concomitant medications (including supplements and over the counter medications)
- Review of inclusion and exclusion criteria
- Urine pregnancy test
- Vital signs, weight, and height

The screening period consists of the Screening 1, 2, 3, and 4 visits. See Figure 4-2 for details of the timing of the screening period visits as well as details of the feminine product dispensation and collection during screening.

The Screening 1 visit will be conducted following the signing of the informed consent form and should occur within 4 days after completion of menses. The Screening 1 visit will include a full medical history (including menstrual history for 3 months prior to Screening and prior uterine imaging assessments), review of inclusion and exclusion criteria, collection of concomitant medications and SAEs, obtaining of clinical evaluations including vital signs, height, weight, temperature, a complete physical examination including visual acuity (not including a gynecological examination), clinical laboratory tests, urinalysis, and a urine pregnancy test will be conducted. Feminine product will be dispensed with instructions to collect and return all product used during the next menses.

Screening 2 visit is scheduled to occur within 4 days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine product to determine if their menstrual blood loss is ≥ 80 mL. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine product will be dispensed for collection of menstrual blood loss during the next menses.

The patient will return for the Screening 3 visit within 10 days of Screening 2 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL. At the Screening 3 visit 3, review of inclusion and exclusion criteria will be conducted confirmation of continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. In addition, the patient will undergo a gynecological examination (a Papanicolaou test must be conducted for women without a test result 6 months prior to the Screening 1 visit). Re-measurement should be performed for inadequate or false-positive results. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. A transvaginal and/or transabdominal pelvic ultrasound with saline or gel contrast will be performed to assess for uterine fibroids. The anatomic location and size of the fibroid disease will be estimated. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to randomization). An endometrial biopsy will be obtained. Bone densitometry by DXA of the lumbar spine, total hip, and femoral neck will be scheduled to be completed prior to randomization for submission to central reader. Patients who will be ≥ 39 years of age at the time of the Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) within 3 months prior to the Screening 1 visit. If not, a mammogram will also be scheduled as a part of Screening 3 visit.

Patients will be provided with the eDiary instructions at this Screening 3 visit and will be dispensed feminine products to be gathered for the second cycle. Each patient will begin recording information into the eDiary including menstrual bleeding and use of feminine products for menstrual bleeding (ie, on the day of Screening 3 visit). The eDiary will be maintained on a daily basis for the duration of the study up until the day before the Week 24 (or Early Termination) visit.

The Screening 4 visit is scheduled to occur within 4 days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be

6.8. Study Procedures

6.8.1. Efficacy-Related Procedures

6.8.1.1. 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. 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.

6.8.1.2. Transvaginal and Transabdominal Ultrasound

Transvaginal with or without transabdominal ultrasound with or without saline or gel contrast is performed for the diagnosis of uterine fibroids, 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. Transvaginal ultrasound will be performed. 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.

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

Uterine or myoma volume = $D1 \times D2 \times D3 \times \pi / 6$
Where:
D1 = the longest diameter of the myoma or uterus (unit of length: cm)
D2 = the longest diameter of the myoma or uterus that is perpendicular to D1 (unit of length: cm)
D3 = the diameter of the myoma or uterus that crosses the intersection of D1 and D2 (intersection "Z") and is perpendicular to the D1/D2 plane (unit of length: cm).

The D1, D2, and D3 locally-determined values for the uterus and myoma will be recorded centrally. The images will be submitted for central review to confirm myoma presence and size. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

6.8.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF.

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

6.8.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one sample of blood will be collected and stored for future pharmacogenomic analyses, unless precluded by local law or regulations. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.8.2. Safety-Related Procedures

6.8.2.1. Weight, Height, Waist Circumference, and Body Mass Index

Patients should have weight and height measured while wearing indoor clothing and with shoes removed. Waist circumference should be measured with a measuring tape wrapped around the narrowest portion of the patient's mid-section.

6.8.2.2. 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.

- 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).

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. 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 baseline 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 which 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 eDiary entries and answers to the UFS-QoL 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 or partner will be reported as described in Section 7.7 and Section 7.8, respectively.

7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of study drug is administered 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 or surgical intervention, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1).

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit approximately 30 days after the last dose of study drug. 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.

Any event occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

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, version 5.0. 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 Version 5.0

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 $\geq$ 3 x ULN.

Any ALT or AST elevation of this degree or greater occurring during the randomized treatment period or the Follow-up visit 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 SAE criteria.** Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 6.

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** the International Normalized Ratio (INR) >1.5
- 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 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

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 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.

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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 Reporting 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:

- 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 PK 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. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

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 (blinded or unblinded, as applicable).

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy reporting 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 6.7.2 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, electrocardiograms 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 (QTc prolongation), hepatic enzyme increases, 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, osteopenia, metabolic bone disease, and prior medical therapy for low bone mineral density.	Bone mineral density will be monitored at the Baseline Day 1, Week 12, and End of Treatment visits and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-gp inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec.	12-lead ECG at Baseline Day 1, Week 12 and End of Treatment 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 LFTs 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 LFTs (AST or ALT > 3 x ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.

- Proportion of women who achieve amenorrhea over the last 35 days of treatment as measured by the alkaline hematin method;
- Time to amenorrhea as measured by the by the alkaline hematin method;
- Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities;
- Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities;
- Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization;
- Change from Baseline to Week 24 in uterine volume; and
- Change from Baseline to Week 24 in uterine fibroid volume.

The analysis methods used for the primary endpoint will be applied to the analyses of the secondary endpoints of proportion of patients who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction in menstrual blood loss volume over the last 35 days of treatment compared between relugolix Group B and placebo Group C, the proportion of patients with amenorrhea over the last 35 days, the proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of at least 1 g/dL at Week 24 and the proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization.

For the secondary endpoints of time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume and time to amenorrhea, time to event will be defined as weeks from randomization 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 and stratified log-rank test will be used to compare each relugolix arm to placebo. Randomization stratification factors will be used to stratify inferential testing.

Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, the Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline. The between treatment comparisons will be performed using model derived least squares means with treatment, stratification factors, baseline result accounted for in the model.

Baseline Numerical Rating Scale score is defined as the average Numerical Rating Scale score from the 35 days of data collected prior to the date of first dose of study drug after randomization. The Numerical Rating Scale score during the final study month is the average Numerical Rating Scale score during the last 35 days on treatment.

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

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

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

Date: _____

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

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

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

During the previous 3 months, how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
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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	During the previous month, 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?	□	□	□	□	□

Appendix 7. Assessment of Abnormal Liver Function 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 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

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

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. At the Screening 1 visit, the longest diameter (D1) of the largest myoma will be noted and recorded. Only the largest myoma among those measurable at the Screening 1 visit will be measured throughout the study.

6.7.1.3. Endometrial Biopsy

An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A second biopsy is to be performed at the Week 24. The biopsies will be read locally, but biopsies may be requested for central review.

6.7.1.4. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.7.1.5). To maintain blinding, concentrations of these hormones should be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.7.1.5. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping

6.7.1.10. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3003), and the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued,

6.7.1.11. Pharmacogenomics Sample Collection

For possible exploratory investigation of markers enabling the prediction of drug response, one 5-mL sample of whole blood will be collected and stored for future pharmacogenomic analyses. All patients will be eligible for collection of the pharmacogenomic sample, however, the sample may only be obtained and stored from patients who provide a separate informed consent form for pharmacogenomic sample collection. Patient participation in the pharmacogenomic research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

If possible, the pharmacogenomic sample should be drawn from consented patients at the Baseline Day 1 visit, but it may be drawn at any time during the study through Week 24 (inclusive). Patients can request their sample to be destroyed at any time. A pharmacogenomic sample should not be collected from any patient who has received comparable bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of pharmacogenomic samples.

6.7.2. Safety-Related Procedures

6.7.2.1. Weight, Height, and Body Mass Index

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

6.7.2.2. 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.

6.7.2.3. 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 the Baseline assessment. Visual acuity will be checked at the beginning and end of the study by a standard visual eye chart. The patient should wear any prescribed glasses or contacts during the visual acuity assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for

4.2. Discussion of Study Design, Including Dosing Rationale and Choice of Control Group

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with heavy menstrual bleeding associated with uterine fibroids. This study will focus on the primary objective of demonstrating a reduction in heavy menstrual bleeding, the most common and burdensome symptom of uterine fibroids. The study is designed to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An extension study is planned to provide additional safety and efficacy data through 48 weeks.

Women with uterine fibroids and heavy menstrual blood loss by the alkaline hematin method of ≥ 80 mL/cycle as assessed during two cycles will be enrolled in this study. Randomization will be 1:1:1. Placebo was selected as the appropriate control for the study because there is no standard of care medical therapy for the long-term treatment of women with uterine fibroids and heavy menstrual bleeding. Commonly-used treatment options range from combined oral contraceptive pills, which are not effective in many cases, levonorgestrel-containing intrauterine devices, and leuprolide therapy indicated for 3 months in the preoperative setting.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. This dose was selected for evaluation in phase 2 clinical studies based upon phase 1 data demonstrating similar estradiol and progesterone suppression in women treated with single doses of relugolix 40 mg or 80 mg, and data demonstrating that premenopausal women treated with multiple doses of 40 mg once daily relugolix over 14 days had estradiol levels suppressed to a median value of 3.68 pg/mL.

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, as described above, a phase 2 study of doses of relugolix 10, 20 and 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

Term	Explanation
PD	pharmacodynamics
P-gp	P-glycoprotein
PGx	pharmacogenomics
PK	pharmacokinetics
PLD	phospholipidosis
QTc	corrected QT interval
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
SD	standard deviation
UFS-QoL	Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)
ULN	upper limit of normal
USP/NF	United States Pharmacopeia and the National Formulary
VAS	visual analogue score
WBC	white blood cells
WHO-DDE	World Health Organization Drug Dictionary Enhanced

	Safety Objectives • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks. Pharmacokinetic and Pharmacodynamic Objectives • To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate
	Exploratory Objectives • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.

Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by centrally-reviewed transvaginal and/or transabdominal ultrasound. Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL each cycle for 2 cycles during the screening period. During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline Day 1 and Week 24 visits, patients will attend visits monthly (ie, every 4 weeks). At the Screening, Week 12, and Week 24 visits, patients will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). An endometrial biopsy will also be performed at Screening. A transvaginal and/or transabdominal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy. Patients will have paired baseline and end-of-treatment endometrial biopsies, independent of ultrasound results. Feminine products will be standardized and will be collected and assessed for blood loss by the alkaline hematin method. Complete blood counts and chemistries will be collected monthly and uterine and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients

Objective(s)	Endpoint(s)
	the alkaline hematin method; • Proportion of women with a hemoglobin below the lower limit of normal at Baseline who achieve an increase of ≥ 1 g/dL from Baseline at Week 24; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for physical activities; • Change from Baseline to Week 24 in the Menorrhagia Impact Questionnaire Score for social and leisure activities; • Proportion of women who achieve a mean Numerical Rating Scale score for uterine fibroid-associated pain over the last 35 days of treatment that is at least a 30% reduction from Baseline in the subset of women with a maximum pain score ≥ 4 during the 35 days prior to randomization; • Change from Baseline to Week 24 in uterine volume; and • Change from Baseline to Week 24 in uterine fibroid volume.
<u>Safety</u>	
• To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate in women with heavy menstrual bleeding associated with uterine fibroids compared with placebo for 24 weeks; • To determine the change in bone mineral density of women with heavy menstrual bleeding associated with uterine fibroids treated with 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low dose estradiol and norethindrone acetate compared with placebo for 24 weeks.	• Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Weeks 12 and 24 in bone mineral density at the spine (average of L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms.
<u>Pharmacokinetic and Pharmacodynamic</u>	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-

Appendix 4. Uterine Fibroid Symptom and Quality of Life Questionnaire

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

	During the previous month, 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?	□	□	□	□	□
10	Made you anxious about traveling?	□	□	□	□	□
11	Interfered with your physical activities?	□	□	□	□	□
12	Caused you to feel tired or worn out?	□	□	□	□	□
13	Made you decrease the amount of time you spent on exercise or other physical activities?	□	□	□	□	□
14	Made you feel as if you are not in control of your life?	□	□	□	□	□
15	Made you concerned about soiling underclothes?	□	□	□	□	□
16	Made you feel less productive?	□	□	□	□	□
17	Caused you to feel drowsy or sleepy during the day?	□	□	□	□	□
18	Made you feel self-conscious of weight gain?	□	□	□	□	□
19	Made you feel that it was difficult to carry out your usual activities?	□	□	□	□	□
20	Interfered with your social activities?	□	□	□	□	□
21	Made you feel conscious about the size and appearance of your stomach?	□	□	□	□	□
22	Made you concerned about soiling bed linen?	□	□	□	□	□

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3001
Location	Multinational, including North and South America, Europe, and Australia
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. <u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Achievement of amenorrhea; o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

and uterine fibroid volumes will be assessed at the Screening and Week 24 visits. Patients will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
4. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal ultrasound performed during the screening period; at least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
   a. Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm (longest diameter), or
   b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3

      Note 1: 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.

      Note 2: Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone;
5. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL during 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period;
6. Patient is not expected to undergo gynecological surgery or ablation procedures for uterine fibroids within the 6 months following enrollment;
7. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
8. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1[b]**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]**	**Baseline Day 1[d]** (if MBL is ≥80 mL/cycle for 2 cycles)	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[e]** (~30 days after last dose of study drug)
Status of Menstruation Recovery													X

Notes:

Abbreviations: EQ-5D, European Quality of Life Five-Dimension Five-Level Scale; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGx, pharmacogenomics; PK, pharmacokinetics; UFS-QoL, Uterine Fibroid Score – Quality of Life

a. The screening period should be initiated after the informed consent form is signed and any required washout for excluded medications or devices is complete.
b. Visit to occur within 4 days of the completion of menses.
c. Visit to occur within 10 days after Screening 2 visit if the menstrual blood loss is determined to be ≥ 80 mL. The Screening 1 or Screening 2 visits for alkaline hematin menstrual blood loss may be repeated at the discretion of the investigator if one menstrual cycle does not meet MBL criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 4 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose PD sample, pregnancy and urinalysis test samples prior to first dose of study drug. The patient must complete MIQ, UFS-QoL, and EQ-5D questionnaires prior to first dose of study drug.
e. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003), a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~4 weeks after an Early Termination visit).
f. Collect serious adverse event information from the time of signed informed consent through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, whichever occurs first.
g. Complete Physical Exam (not including a gynecological examination). Visual acuity must be assessed with a standard eye chart. The patient should wear any prescription glasses or contacts during the assessment.
h. Papanicolaou test must be conducted for women without a test result 6 months prior to the Screening 1 visit. Re-measurement should be performed for inadequate or false-positive results.
i. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state for the Baseline and Week 24 visit clinical laboratory tests.
j. At the Baseline Day 1 visit (clinical laboratory tests in fasted state), in addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, iron, ferritin, and hemoglobin A1c. An additional sample will be collected at this visit and stored for possible future testing for presence of hepatitis A, B, and C if required per request from medical monitor to assess etiology of liver test abnormalities.
k. At the Week 24 visit or Early Termination visit (clinical laboratory tests in fasted state), in addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.

Objective(s)	Endpoint(s)
Pharmacokinetic and Pharmacodynamic	
• To evaluate the pharmacokinetic (PK) and pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.	• Pre-dose trough concentrations (C_τ) of relugolix, estradiol, and norethindrone from Baseline through Week 24; • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.
Exploratory	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or the placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (up to ~13 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns and as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by a centrally-reviewed transvaginal ultrasound (with or without a transabdominal ultrasound). Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for 2 cycles or

Figure 4-1 MVT-601-3001 Study Schematic

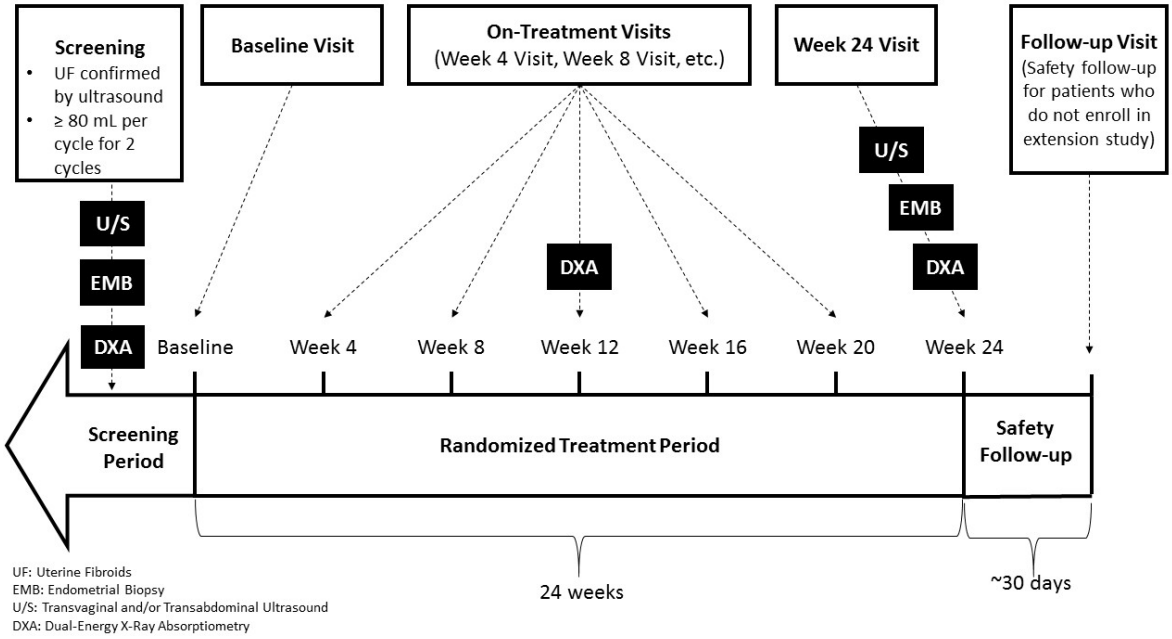
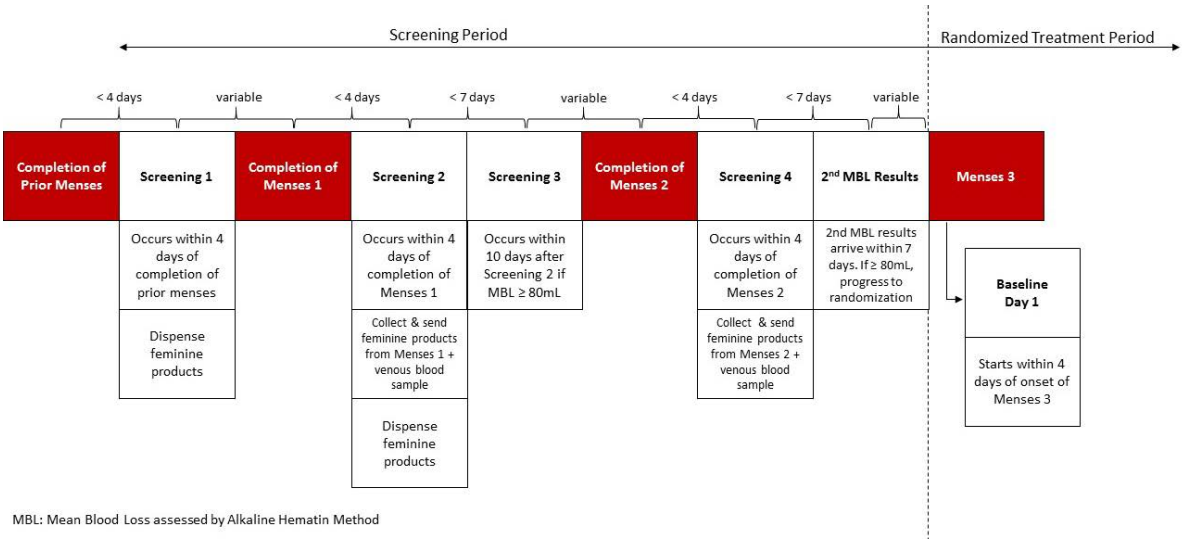


Figure 4-2 Schematic of MVT-601-3001 Screening Visits and Feminine Product Dispensation and Collection during the Screening Period



density loss unacceptable for long-term treatment. This phase 3 study will primarily assess the efficacy and safety of relugolix 40 mg co-administered with a low-dose of estradiol and norethindrone acetate compared with placebo at 24 weeks 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. An additional arm with monotherapy relugolix administered for 12 weeks followed by 12 weeks of relugolix co-administered with low-dose hormonal add-back therapy is included to provide data on the requirement for hormonal therapy to mitigate the adverse relugolix side effects of bone mineral density loss and hot flushes.

All eligible women who complete the 24-week study will be offered the opportunity to enroll in an open-label extension study to obtain long-term safety and efficacy data over an additional 24 weeks of treatment, providing approximately 1 year of safety data on the women originally randomized to relugolix.

4.3. Selection of Study Population

The study population will include approximately 390 premenopausal women aged 18 to 50 years with heavy menstrual bleeding (≥ 80 mL over 2 cycles by the alkaline hematin method) associated with uterine fibroids demonstrated over two cycles 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 randomization and enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Baseline Day 1 visit, unless otherwise specified:

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);
4. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
5. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal ultrasound performed with saline or gel contrast during the screening period. At least one uterine fibroid must be verified by a central reader to meet at least one of the following criteria:
    a. Subserosal, intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter), or
    b. Multiple small fibroids with a total uterine volume of ≥ 130 cm^3;

- Ultrasound – do not proceed with additional procedures if no uterine fibroids are identified with the local/initial reading
- Gynecology examination, Papanicolaou test (if need), endometrial biopsy
- Clinical laboratory tests, urinalysis
- Dispense feminine products and paper diary with instructions to begin recording starting information daily, starting on the Screening 1 visit day
- Schedule mammogram (if needed)
- Schedule bone densitometry

The ultrasound will be a transvaginal ultrasound (with or without a transabdominal ultrasound (see Section 4.3 ultrasound entry criteria), performed to assess for uterine fibroids. Saline or gel contrast may be used but is not required (see Section 4.3 ultrasound entry criteria). The anatomic location and size of the fibroid disease will be estimated by the local reader. The ultrasound images will be submitted to the central reader for confirmation that the patient meets the inclusion criteria for a diagnosis of uterine fibroids (this confirmation must be received prior to randomization). The investigator, rather than the central reader, will determine if any exclusionary pathology is present. If ultrasound fails to demonstrate fibroids on the local reading, do not proceed with additional Screening visit 1 procedures.

The Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit and the specimen is to be submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

The endometrial biopsy will be obtained using a pipelle and submitted to the Central Laboratory.

The mammogram must be done in patients ≥ 39 years of age by the time of the (anticipated) Baseline Day 1 visit if there is no record (and reading) from within 6 months prior to the screening period.

6.2.2. Screening 2 Visit

Screening 2 visit is scheduled to occur within 5 (+2) days after cessation of the patient's first menses following the Screening 1 visit. Patients will return at Screening 2 visit to return their feminine products. At this visit, clinical laboratory tests will be drawn, including a venous blood sample for use in the quantitation of menstrual blood loss. Additional feminine products will be dispensed for collection of menstrual blood loss during the next menses. If the hemoglobin is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be obtained as an unscheduled test. Women whose laboratory testing reveals iron-deficiency anemia as defined in the study must be started on iron therapy.

Confirm the scheduling of the bone densitometry and mammogram (if needed) and review mammogram results, if available. The mammogram must be normal (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) in order for the patient to be eligible.

Once the menstrual blood loss results from the first cycle are available, schedule Screening 3 visit as soon as feasible and within 5 (+2) days of receiving results showing that the menstrual blood loss is ≥ 80 mL.

Patients will be dispensed feminine products to be gathered for the second cycle.

collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn for hemoglobin assessment. The patient's eDiary data collection will be reviewed. Laboratory and imaging evaluations will be reviewed to ensure eligibility for randomization.

At the discretion of the investigator, the Screening 1 or 2 visits can be repeated if one menstrual cycle does not meet the heavy menstrual bleeding alkaline hematin criteria and it is thought to be due to an inadequate collection by a highly motivated patient. A Randomization Authorization Form must be submitted to the sponsor for approval prior to conducting the Baseline Day 1 visit. The Baseline Day 1 visit should be scheduled to coincide as closely as possible to when the patient will be finished with her next menses.

6.3. Randomized Treatment Period (Baseline to Week 24)

At the Baseline Day 1 visit, patients will be randomized to one of the three study treatment arms (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the Week 24 visit. Patients will continue recording daily in their eDiary. On-treatment study visits will occur every 4 weeks through the end of Week 24. At each post-baseline visit, patients will return their feminine products for alkaline hematin testing. Safety monitoring including signs and symptoms directed physical examination, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12 and 24 visits. A repeat transabdominal and/or transabdominal ultrasound and endometrial biopsy will be performed at the Week 24 visit. The endometrial biopsy will be read locally. Study drug and eDiary compliance will be reviewed at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the randomized treatment period.

Sites should try to schedule patient visits during the morning, instructing patients to arrive before taking their study drug to allow for pre-dose PK/PD sampling. Patients should come to the clinic in the fasted state (eg, nothing to eat or drink after midnight the day before the clinic visit).

6.4. Continuation into Extension Study

It is expected that most patients will enter the 24-week extension study (MVT-601-3003), which will be conducted under a separate protocol. Patients will provide separate informed consent to participate in the extension study during which all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate.

6.5. Follow-up Visit

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3003), will have a 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 or surgical intervention, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation. Patients who withdraw early from this study will also undergo the Follow-up visit approximately 30 days after the last dose of study drug, or the date of initiation of another

Saline or gel contrast is not required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone or when endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (eg, suspected intrauterine masses, equivocal endometrial findings, etc.). If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24.

6.8.1.3. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. For PK analysis of estradiol, a separate PK sample will be obtained to be analyzed at a PK laboratory (see Section 6.8.1.4). To maintain blinding, concentrations of these hormones will be reported to the investigator, other vendors, and sponsor personnel only after database lock and unblinding.

6.8.1.4. Pharmacokinetics Sample Collection

Blood samples for PK analysis of relugolix, estradiol, and norethindrone will be collected pre-dose at the visits indicated in the study Schedule of Activities in the protocol synopsis (see Section 1.1). The actual date and time of each blood sample collection will be recorded.

Patients will be instructed to hold their dose of study drug on clinic visit days and record the time of their previous dose (ie, the time they took their dose on the day before the clinic visit). If the study patient inadvertently took drug at home on the morning of the clinic visit, the dosing history should be accurately recorded and a PK sample collected (which may be used for population PK modeling).

To maintain blinding, PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding. Collection, processing, storage, and shipping procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.8.1.5. Patient Diary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. Patients will complete daily eDiaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

6.8.2.3. 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 the Baseline assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 2 years prior to the Screening 1 visit and submitted to the central laboratory. A repeat test should be performed for inadequate or false-positive results and submitted to the central laboratory.

6.8.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (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.

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 serious adverse event 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 and events of overdose or pregnancy is available on the Serious Adverse Event report form. Information may also be provided to PPD

The initial report should include:

- Study number (MVT-601-3001)
- Site name and number
- Investigator name
- Patient ID 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 and whether or not the cause of death was related to study drug, 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:

Send completed Safety Report Forms to PRA Safety & Risk Management:

Site Location	E-mail (Primary reporting method)	Fax Number (Secondary reporting method)
North/South American sites:	PPD	PPD or PPD
Europe, Asia, Pacific and Africa sites:		PPD

For questions on Serious Adverse Event (SAE)/Adverse Event of Clinical Interest (AECI) reporting, please call:

- North/South America: PPD or PPD
- Europe, Asia, Pacific, and Africa: PPD

The initial report should include:

- Study number (MVT-601-3001)
- Site address and number
- Investigator name
- Patient ID 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.

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; visual acuity will be checked at the beginning and end of the 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.	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.	Monthly pregnancy testing; 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, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	Clinical chemistries assessing LFTs, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

9.4. Safety Analyses

Safety analyses will be conducted using the safety population and summarized by treatment group as treated. The treatment emergent period will be defined as the period of time from the first dose date of study drug through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy or surgical intervention, 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, version 5.0. All adverse events will be coded to preferred term and system organ class using MedDRA 12.0 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, v. 5.0 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 baseline versus post-baseline results. All data will be listed and summarized by visit. The change from baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

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

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), T-score for average of L1-L4, total hip, and femoral neck. All data will be listed and summarized by visit. The change, percent change from Baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

All data will be listed and summarized by visit. The change, percent change from baseline to Weeks 12 and 24 and associated 95% confidence intervals will be presented by treatment group for each parameter.

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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Appendix 5. 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 ❑

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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.

procedures are provided in the Study Reference Manual. Plasma and serum analysis will be performed by the sponsor (or designee).

Plasma concentrations of relugolix and norethindrone and serum concentrations of estradiol will be determined in samples using a validated bioanalytical methodology. Raw data will be archived at the bioanalytical site. Once a sample has been analyzed for relugolix, estradiol, or norethindrone, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

6.7.1.6. Patient eDiary

All women enrolled in the study will be provided with a device with an application for a patient eDiary, along with detailed instructions for its use. During menstruation, patients will complete daily diaries including compliance with study treatment, menstrual bleeding, use of feminine products, uterine fibroid-associated pain, and use of pain medication (analgesics) to treat uterine fibroid pain (see Appendix 2).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will act as its own source data and these data will be reviewed by the investigator to identify any potential adverse events.

6.7.1.7. Menorrhagia Impact Questionnaire

The Menorrhagia Impact Questionnaire (MIQ) 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 3). The MIQ has undergone psychometric validation. Patients will complete the MIQ at each study visit during the randomized 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.

6.7.1.8. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom – Quality of Life (UFS-QoL) score is used to evaluate the symptom severity and the quality of life of patients with uterine fibroids (see Appendix 4). Patients will complete the UFS-QoL questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

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

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

Patients will complete the EQ-5D questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit before other study procedures, such as blood draws and physical examinations, are performed.

women without an available test result from within 6 months prior to the Screening 1 visit. Re-measurement should be performed for inadequate or false-positive results.

6.7.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Reference Manual and the protocol Schedule of Activities in the synopsis (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	White Blood Cell (WBC) Count	Qualitative
Chloride	WBC Differential	Protein
Bicarbonate	Red Blood Cell Count	Glucose
Blood Urea Nitrogen	Hemoglobin	Occult blood
Creatinine	Hematocrit	Urobilinogen
Glucose	Mean Corpuscular Volume	Bilirubin
Calcium	Platelet Count	Pregnancy test
Phosphate		(human chorionic gonadotropin)
Magnesium		
Albumin		
Total Protein		
Alkaline Phosphatase		
Lactate Dehydrogenase		
Creatine Kinase		
Liver Function Tests including:		
Bilirubin Total		
Alanine Aminotransferase		
Aspartate Aminotransferase		
Gamma-Glutamyl Transferase		
Lipid Profile including:		
Total Cholesterol		
Low Density Lipoprotein		
High Density Lipoprotein		
Triglycerides		

1. PROTOCOL SYNOPSIS

Study Title	An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Number	MVT-601-3001
Location	Multinational, including North and South America, Europe, and Australia
Study Centers	Approximately 120 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 50 years diagnosed with heavy menstrual bleeding associated with uterine fibroids
Number of Patients Planned	Approximately 390 (~ 130 relugolix co-administered with low-dose estradiol and norethindrone acetate, ~ 130 relugolix monotherapy followed by relugolix co-administered with low-dose estradiol and norethindrone acetate, and ~ 130 placebo)
Study Objectives	<u>Primary Efficacy Objective</u> • To determine the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids. <u>Secondary Efficacy Objectives</u> • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on heavy menstrual bleeding associated with uterine fibroids; • To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo for 24 weeks on the following: o Change in hemoglobin; o Impact of heavy menstrual bleeding on social, leisure, and physical activities; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

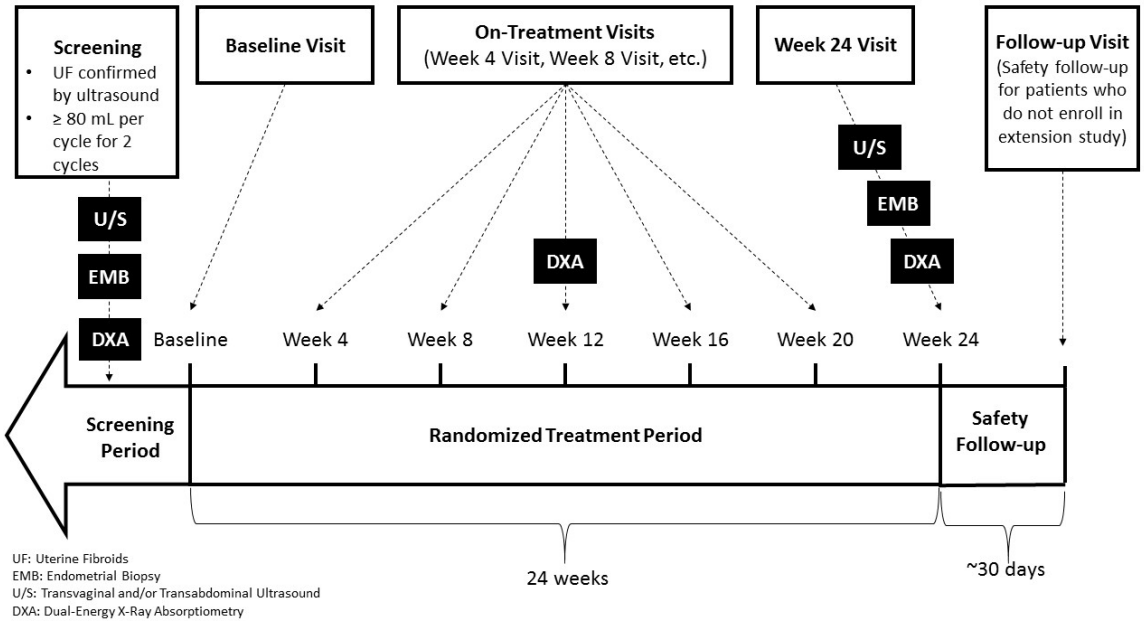
will complete daily electronic diaries (eDiary) including compliance with study treatment, menstrual bleeding, use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medication to treat pain caused by uterine fibroids. Quality of life questionnaires will be completed according to the Schedule of Activities.

Safety will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Height will be measured at the Screening 1 visit and weight will be measured at specified intervals.

Samples will be collected for PK assessment of relugolix, estradiol, and norethindrone and for the pharmacodynamic assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone.

All patients completing the Week 24 visit, including women randomized to placebo, will be offered the opportunity to enroll in an open-label extension study in which all eligible patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a follow-up visit approximately 30 days after the end of treatment (ie, after the patient's last dose of study medication).

Study Schematic



Inclusion/Exclusion Criteria

Inclusion Criteria (all inclusion criteria must have been met prior to randomization unless otherwise specified):

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing and dating the informed consent form;
3. Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);
4. Has regularly-occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by patient history for at least 3 months prior to the Screening 1 visit;
5. Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal

Objective(s)	Endpoint(s)
low-dose estradiol and norethindrone acetate.	dose concentrations of LH, FSH, estradiol, and progesterone.
Exploratory	
• To determine the benefit of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on patient-reported quality of life outcome measures.	• Change from Baseline to Week 24 in the Uterine Fibroid Scale – Quality of Life Symptom Severity and Health-related Quality of Life subscales comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively; • Change from Baseline to Week 24 in the European Quality of Life Five-Dimension Five-Level scale comparing each relugolix treatment group to placebo inferentially and the two relugolix groups descriptively.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

This study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate and 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with 24 weeks of placebo. Approximately 390 women with heavy menstrual bleeding associated with uterine fibroids will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A; N ≈ 130), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B; N ≈ 130), or the placebo group (Group C; N ≈ 130). Stratification variables will include: geographic region (North America versus Rest of World) and mean screening menstrual blood loss volume (< 225 mL versus ≥ 225 mL) by the alkaline hematin method.

The study consists of a screening period (~11 weeks), a randomized treatment period (24 weeks), and a follow-up period (~30 days). Additionally, unscheduled follow-up visit(s) may be arranged for patients with study-related safety concerns as needed.

A diagnosis of uterine fibroids will be confirmed during the screening period by a centrally-reviewed transvaginal and/or transabdominal ultrasound. Heavy menstrual bleeding will be defined as menstrual blood loss of ≥ 80 mL per cycle for each of 2 cycles during the screening period. During the randomized treatment period, study participants will take blinded study drug orally once daily for 24 weeks. Women with iron-deficient microcytic anemia with a hemoglobin ≤ 10 g/dL at Screening must be treated with oral or parenteral iron replacement therapy. Between the Baseline and Week 24 visits, patients will attend visits monthly (ie, every