Study Title:	LIBERTY 2: 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
NCT Number:	03103087
Document Date:	Protocol Original: 10-NOV-2016 Protocol Amendment 1: 10-FEB-2017 Protocol Amendment 2: 25-SEP-2017

16.1. Study Information

16.1.1. Protocol and Protocol Amendments

16.1.1.1. Original Protocol

16.1.1.2. Amendment 1

16.1.1.3. Amendment 2

CLINICAL STUDY PROTOCOL

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
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
IND #:	131161
Version:	Original
Effective Date:	10-Nov-2016

SPONSOR SIGNATURE PAGE

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-601-3002

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

PPD

16 Nov 2016
Date

10 Nov 2016
Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

Myovant Sciences GmbH 4 CONFIDENTIAL

TABLE OF CONTENTS

Myovant Sciences GmbH 6 CONFIDENTIAL

Myovant Sciences GmbH 7 CONFIDENTIAL

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
EQ-5D	European Quality of Life Five-Dimension Five-Level
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menstrual Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart

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

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-601-3002
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.

	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 transabdominal and/or or transvaginal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized. 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

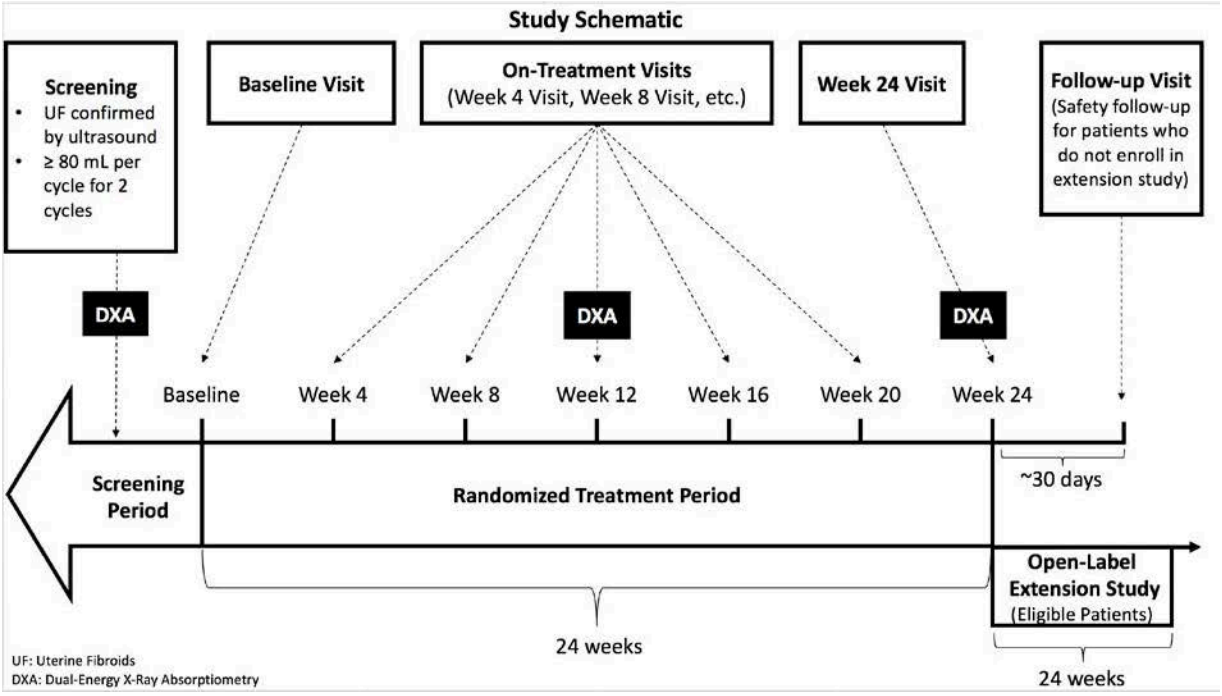
Myovant Sciences GmbH 13 CONFIDENTIAL

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 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;
6. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period;
7. Patient does not desire and is not expected to be a candidate for gynecological surgery or ablation procedures within the 6 months following enrollment;
8. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
9. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during any required washout for excluded medications (if applicable), the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
10. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer);
11. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period;
12. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment;
2. Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine or total hip;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;

7. Has a history of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Calculated creatinine clearance < 60 mL/min using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina;
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at

	any screening visit or the Baseline Day 1 visit; h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram; 15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit; 16. Has a history of clinically significant condition(s) including, but not limited to the following: a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded); b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma; c. History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year); 17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study; 18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable washout periods from these medications are also described therein); 19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form); 21. Has participated in a previous clinical study that included the use of relugolix; 22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling); 23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.
Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, color, and odor for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, color, and odor will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, color, and odor.

Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. <u>Primary Efficacy Endpoint</u> • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35days 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. Safety Endpoints • 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. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (Cτ) 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 Endpoints • 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.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women 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 on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the 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, a sample size of 260 (130 patients in each of the relugolix and placebo arms) will provide $> 99\%$ power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, endometrial biopsies, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be

presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE, version 5.0. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4),), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3002

	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)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)	**Within 4 days after completion of menses**	**Within 4 days after completion of Screening 1 menses**	**Within 10 days of Screening 2 visit**	**Within 4 days after completion of 2nd Screening menses**	**Within 4 days of the start of menses**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X	X
Height	X												
Weight	X				X						X	X	X
Temperature	X				X						X	X	
Adverse Event Collection[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination, Including Visual Acuity[g]	X				X						X		
Gynecologic Examination with Pap Test, if applicable			X[h]								X		

Myovant Sciences GmbH 22 CONFIDENTIAL

	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	

Myovant Sciences GmbH 23 CONFIDENTIAL

	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

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.
l. For an Unscheduled visit, a central safety laboratory assessment or PK sample collection is performed as needed.
m. Pharmacokinetics samples: Samples should be obtained in the fasted since study drug is administered on an empty stomach. Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete (with the exception of Week 24 when no dose is administered).
n. Pharmacodynamic samples: Samples should be obtained in the fasted since study drug is administered on an empty stomach, collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Instruct the patient not to take her study treatment at home on these visit days. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Screening 1 visit, Week 24 and Follow Up visits when no dose is administered).
o. Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive).
p. Patients ≥ 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) during the screening period or within 3 months prior to the screening period; if not, schedule at the Screening 3 visit.
q. Transvaginal or transabdominal ultrasound with saline or gel contrast must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps. Results must be submitted to and confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is the preferred procedure. A transabdominal ultrasound may also be obtained if indicated, for example, by extension of large masses outside the pelvis.
r. Endometrial biopsy is performed at Screening after the first acceptable alkaline hematin sample collection.
s. Endometrial biopsy is to be performed at the Week 24 visit if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized) and may be requested for central review if abnormal.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results available prior to randomization.
u. Randomization: After a patient is screened and the investigator determines that the patient is eligible for randomization the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's randomization in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit.
v. Patient electronic diary: Patients enter diary information on a daily basis for their compliance with (study treatment starting at Baseline/Day 1), menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening visit 2 and compliance with study treatment starting at Baseline/Day 1 through Week 24 or early termination.
w. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.

Myovant Sciences GmbH 25 CONFIDENTIAL

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

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

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

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which are

Myovant Sciences GmbH 26 CONFIDENTIAL

administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

Myovant Sciences GmbH 27 CONFIDENTIAL

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

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 µg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 µg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 µg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥100 mg/kg (estimated C_{max} of 4.0 µg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 µg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and three phase 2 studies (including one in women with uterine fibroids and two in women with endometriosis) have been completed. In addition, six clinical studies evaluating relugolix are ongoing, including two phase 1 studies, two phase 2 studies in men with prostate cancer (US and Europe), and two phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least one dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

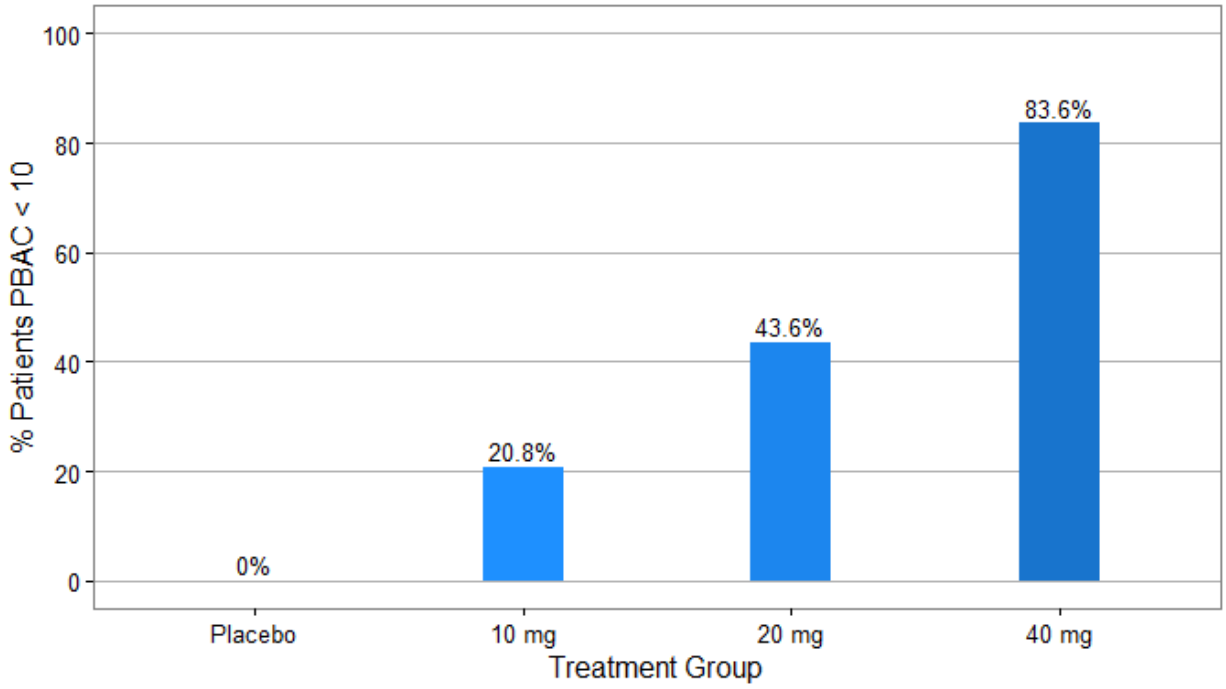
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 45%. The exposure of relugolix is increased by inhibitors of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of

cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver function test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Myovant Sciences GmbH 31 CONFIDENTIAL

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 interim analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤50 ng/dL) and maintained these levels through at least 24 weeks. These data are comparable to testosterone levels achieved by leuprolide 22.5 mg every 3 months. Study C27003 demonstrated rapid and sustained suppression of testosterone levels for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, Version 9.0, dated 09 November 2016, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
Primary Efficacy	
• 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.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
Secondary Efficacy	
• 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.	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • 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

Myovant Sciences GmbH 33 CONFIDENTIAL

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-

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 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

Myovant Sciences GmbH 35 CONFIDENTIAL

transabdominal and/or or transvaginal ultrasound will be performed at Week 24, followed by a repeat endometrial biopsy if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized). 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.

Figure 4-1 MVT-601-3002 Study Schematic

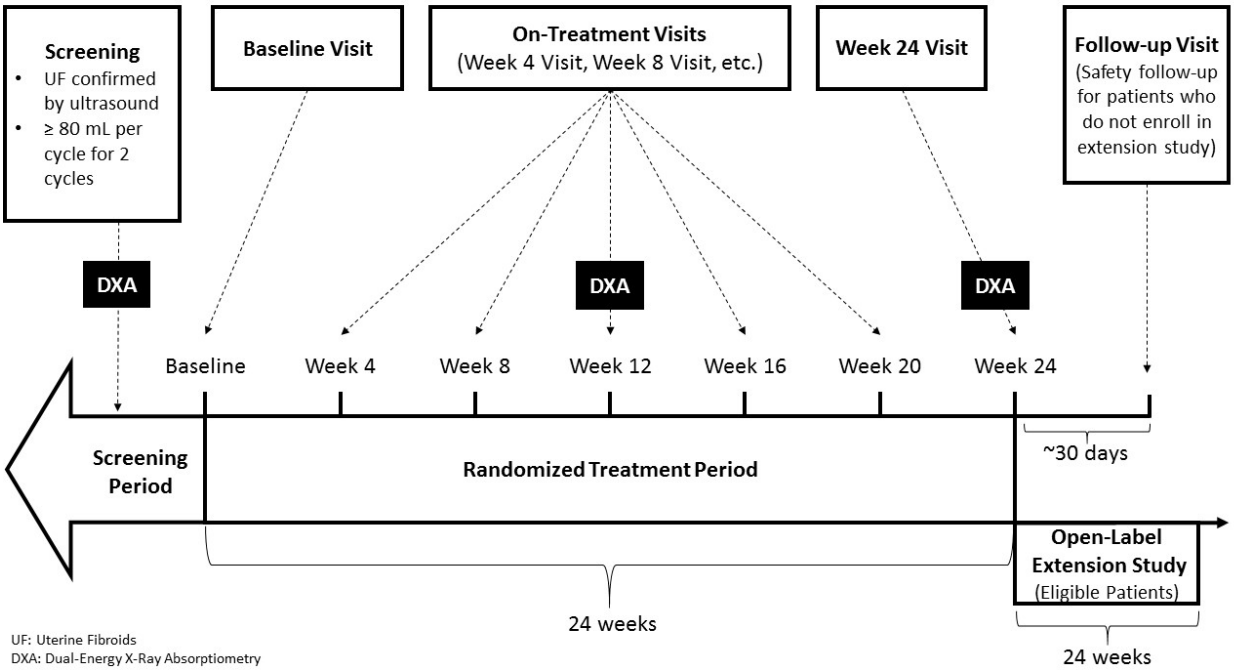
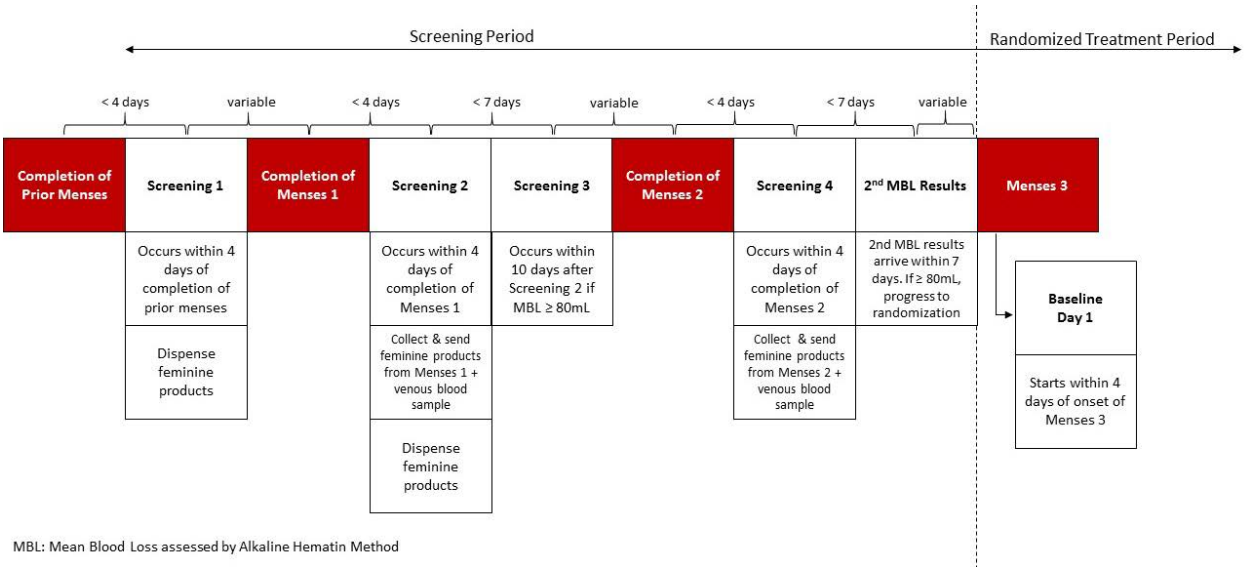


Figure 4-2 Schematic of MVT-601-3002 Screening Visits and Feminine Product Dispensation and Collection during the Screening Period



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 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

Myovant Sciences GmbH 38 CONFIDENTIAL

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 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;
6. Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period;
7. Patient does not desire and is not expected to be a candidate for gynecological surgery or ablation procedures within the 6 months following enrollment;
8. Has a negative urine pregnancy test at the Screening 1, Screening 3, and Baseline Day 1 visits;
9. Agrees to use two forms of non-hormonal contraception (dual contraception, as described in Section 4.7) consistently during any required washout for excluded medications (if applicable), the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
10. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer);
11. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period;

12. A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment;
2. Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine or total hip;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin/calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);

Myovant Sciences GmbH 41 CONFIDENTIAL

12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Calculated creatinine clearance < 60 mL/min using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina;
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year);

17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable washout periods from these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

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

After a patient is screened and the investigator determines that the patient is eligible for enrollment, the site staff will complete the Randomization Authorization Form and send it to the sponsor (Myovant Sciences GmbH) or sponsor designee per the instructions in the Study Reference Manual. The sponsor (or designee) will approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's Baseline Day 1visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient Identification Number.

4.6. Removal of Patients from Therapy

Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Patients who have percent change from Baseline in bone mineral density at either the Week 12 or Week 24 visit (or any unscheduled visit) at the lumbar spine (average L1-L4), total hip, or femoral neck of < -4.0 that is repeated and confirmed (ie, both values are < -4.0);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.6 for information on pregnancy reporting).

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

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram);
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of dual contraception are:

- Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process and will confirm when they sign a consent form they understand the requirements for avoidance of pregnancy during the course of the study. Patients may not donate ova during the course of the study and for 1 month following the last study visit.

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

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

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

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

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

Table 5-1 Description of MVT-601-3002 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An over-encapsulated round film-coated white tablet with placebo back-fill material	Capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 12 or 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

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

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

5.2.1. Product Characteristics

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

Placebo to match relugolix is a pink tablet using USP/NF excipients.

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

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3002 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with relugolix placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

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

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

Patients should take any oral iron supplementation with meals.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK/PD samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event.

Patients may subsequently be re-started on study drug, with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 1°C to 30°C until it is used or returned to the sponsor (or designee). A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

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

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

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

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment, however, the Investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options **before** unblinding the patient's treatment assignment. If unblinding occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient, unless that information is important for the safety of patients currently in the study. Patients whose treatment assignment has been unblinded will be permanently discontinued from treatment.

Myovant Sciences GmbH 48 CONFIDENTIAL

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

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and prior to each visit, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused stud drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

This table provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Washout Periods

Drug Class	Examples	Washout Period/Comments
Bisphosphonates	alendronate etidronate	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	1 month
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone	2 months (6 months for depot subcutaneous or intramusclar injections)

Drug Class	Examples	Washout Period/Comments
Estrogens	estradiol valerate conjugated estrogens	2 months (6 months for depot subcutaneous or intramusclar injections)
Oral Contraceptives	combined or progestin only	2 months
Selective Estrogen Receptor Modulators	raloxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	2 months
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin, calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	2 months
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin tranexamic acid vitamin k preparations	1 month
Glucocorticoids	prednisolone or prednisone dexamethasone	No washout Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction Short duration ($\leq$ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	carbamazepine rifampin St John's wort	2 weeks

Myovant Sciences GmbH 50 CONFIDENTIAL

Drug Class	Examples	Washout Period/Comments
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporin diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir/ritonavir quercetin quinidine ranolazine ticagrelort verapamil	2 weeks (6 months for amiodarone)

Abbreviation: GnRH, gonadotropin-releasing hormone

5.10.2. Permitted Medications

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

5.10.2.1. Analgesics

Use of analgesics is **ONLY permitted under the following conditions** from the Screening 1 visit to the Week 24 (or Early Termination) visit:

- Ibuprofen or other non-steroidal anti-inflammatory medications can be used as the first choice medicine for pain **associated with uterine fibroids**. Narcotic analgesics should be used for severe pain that cannot otherwise be controlled.
- Acetaminophen can be used as the first choice medicine for treatment of an adverse event or other pain **NOT associated with uterine fibroids** such as headache or a common cold.
- Analgesics for topical/external use are also permitted.
- Codeine that is not intended to relieve pain associated with uterine fibroids (eg, codeine phosphate in a combination cold remedy) is permitted.

This restriction was set because analgesic medications are likely to have an impact on the evaluation of a secondary endpoint regarding pain. Analgesics refer to drugs containing compounds that have indications for pain symptoms in the package inserts and antispasmodic drugs that possess indications for gynecological or urological disease in the package inserts.

Myovant Sciences GmbH 51 CONFIDENTIAL

Patients should be instructed not to use analgesics for prophylactic purposes. Patients should also be instructed to record in the eDiary their worst pain symptoms during the past 24 hours before taking analgesics.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL but ≤ 10 g/dL, a mean corpuscular volume below normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.7. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities 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

Pre-screening evaluation, not including any study procedures or tests, may be conducted prior to the initial formal screening evaluation at the Screening 1 visit in an effort to identify patients unlikely to meet study-related entry criteria. Review of medical history, menstrual history, and prior uterine imaging assessments is permitted. 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 cycle) 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 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 collected to submit for the quantitation of menstrual blood loss, and a blood sample will be drawn

Myovant Sciences GmbH 53 CONFIDENTIAL

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 investigational agent or hormonal therapy or surgical intervention, whichever occurs first. Refer to

the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits conducted to evaluate adverse events: vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment and PK sample if indicated, 12-lead ECG, recording of concomitant medications, and study drug compliance.

6.7. Study Procedures

6.7.1. Efficacy-Related Procedures

6.7.1.1. 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.

6.7.1.2. Transvaginal and/or Transabdominal Ultrasound

Transvaginal and/or transabdominal ultrasound with 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 physician (investigator or sub-investigator) will be assigned to a patient and will perform each of the ultrasound scans using the same device as far as possible. Transvaginal ultrasound is preferred, but transabdominal ultrasound may be used as necessary for full visualization of the uterus. The ultrasound method used at screening should be repeated for the ultrasound at the Week 24 visit.

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 if indicated (endometrial thickness at any location is ≥ 4 mm or if any other abnormality is visualized). 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 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.

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 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		

Specialized Hormonal Assessments: Thyroid-Stimulating Hormone Parathyroid Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Iron (Baseline only) Ferritin ((Baseline only) Hemoglobin A1c (Baseline and Week 24 only)		

A separate sample will be collected at the Day 1 visit and will be banked and tested for presence of hepatitis A, B, and C (hepatitis A antibody, IgM, hepatitis B core antibody, IgM, hepatitis B surface antigen, and hepatitis C antibody) if requested by the medical monitor for evaluation of abnormal liver function tests.

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

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

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

6.7.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.7.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient).

The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): 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, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.

6.8. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of 5 mL of whole blood collected for pharmacogenomics testing (see Section 6.7.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

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

7.1. Adverse Event Definitions

7.1.1. Adverse Event

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

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;

- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

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

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

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.

Myovant Sciences GmbH 63 CONFIDENTIAL

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 ≥ 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

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-601-3002)
- 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:

- 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.
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.

Myovant Sciences GmbH 69 CONFIDENTIAL

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
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.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

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

8.2. Monitoring

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

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

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

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

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

Myovant Sciences GmbH 71 CONFIDENTIAL

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥225 mL.

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

9.2. Analysis Populations

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

The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations. The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

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

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 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.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the 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, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;
- 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;

Myovant Sciences GmbH 73 CONFIDENTIAL

- 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.

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.

Myovant Sciences GmbH 74 CONFIDENTIAL

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

The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5% or 6% by body area (lumbar, total hip, and femoral neck) will be estimated with 95% confidence intervals by treatment group. The number and percentage of patients meeting a T-score of < -2.5 by body area will also be estimated with 95% confidence interval by treatment group. Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.5. Pharmacokinetic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

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

- Change from 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.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

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

10.1.4. Confidentiality

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

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

prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

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

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

All clinical study documentation must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and

until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

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

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

10.1.7. Electronic Case Report Forms

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

10.1.8. Investigational Product Accountability

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

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor,

the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

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

10.1.9. Inspections

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

10.1.10. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

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

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

10.2.2. Study Report

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

10.2.3. Posting of Information on Publically Available Clinical Trial Registers

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

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

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

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

10.3.2. Access to Information for Auditing or Inspections

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

10.3.3. Study Discontinuation

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

10.3.4. Publications

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

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

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

Myovant Sciences GmbH 81 CONFIDENTIAL

The investigator will submit to the sponsor any proposed publication or presentation along with the respective target scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The investigator will comply with sponsor requests to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

REFERENCES

ACOG Practice Bulletin No. 96: Alternatives to Hysterectomy in the Management of Leiomyomas. Obstetrics & Gynecology 2008;112(2 Part 1):387-400.

Activella FDA Clinical Pharmacology Review. November 1998. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20907.cfm. Accessed: 16 August 2016.

Activella US Prescribing Information. Revised 10/2013. Available at: http://www.novo-pi.com/activella.pdf. Accessed: 06 August 2016.

Archer DF, Chwalisz K, Feldman R, Stewart EA, Lukes AS, North J, Gao J, Williams LA, Jain R. Elagolix for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UF): Results from a phase 2A proof-of-concept study. American Society for Reproductive Medicine (Oct 17-21). October 20, 2015. Abstract O-181, available at: http://www.fertstert.org/article/S0015-0282(15)00717-7/pdf. Accessed: 08 July 2016.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. American Journal of Obstetrics and Gynecology 1992;166(2):740-5.

Cardozo ER. The estimated annual cost of uterine leiomyomata in the United States. American Journal of Obstetrics and Gynecology 2012;206(3):0092-0100.

Carr BR, Marshburn PB, Weatherall PT, Bradshaw KD, Breslau NA, Byrd W, Roark M, Steinkampf MP. An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial. Journal of Clinical Endocrinology & Metabolism 1993;76(5):1217-23.

Chwalisz K, Surrey E, Stanczyk FZ. The hormonal profile of norethindrone acetate: rationale for add-back therapy with gonadotropin-releasing hormone agonists in women with endometriosis. Reproductive Sciences 2012;19(6):563-71.

Food and Drug Administration (FDA). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. US Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. July 2009.

Franke HR, van de Weijer PHM, Pennings TMM, van der Mooren MJ. Gonadotropin-releasing hormone agonist plus add-back' hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. Fertility and Sterility 2000;74(3):534-539. Available at: http://www.fertstert.org/article/S0015-0282(00)00690-7/pdf. Accessed: 16 August 2016.

Gliklich RE, Leavy MB, Velentgas P, Campion DM, Mohr P, Sabharwal R, Whicher D, Myers ER, Nicholson WK. Identification of Future Research Needs in the Comparative Management of Uterine Fibroid Disease. A Report on the Priority-Setting Process, Preliminary Data Analysis, and Research Plan. Effective Healthcare Research Report No. 31. (Prepared by the Outcome DEcIDE Center, under Contract No. HHSA 290-2005-0035-I, TO5). AHRQ Publication No. 11- EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available at: http://effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed: 16 August 2016.

Hallberg L, Nilsson L. Determination of menstrual blood loss. Scand J Clin Lab Invest. 1964;16(2):244–248.

Hapangama DK, Bulmer Judith N. Pathophysiology of heavy menstrual bleeding. Women's health 2016;12(1):3-13.

Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide Acetate Depot and Hormonal Add-Back in Endometriosis: A 12-Month Study. Obstetrics & Gynecology 1998;91(1):16-24.

Lee DY, Park HG, Yoon BKoo, Choi D. Effects of different add-back regimens on hypoestrogenic problems by postoperative gonadotropin-releasing hormone agonist treatment in endometriosis. Obstetrics & gynecology science 2016;59(1):32-8. Available at: http://synapse.koreamed.org/Synapse/Data/PDFData/3021OGS/ogs-59-32.pdf. Accessed: 16 August 2016.

Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2006;(2):CD003855.

Marret H, Fritel X, Ouldamer L, Bendifallah S, Brun J.L, De Jesus I, Derrien J, Giraudet G, Kahn V, Koskas M, Legendre G, Lucot J.P, Niro J, Panel P, Pelage J.P, Fernandez H. Therapeutic management of uterine fibroid tumors: updated French guidelines. European Journal of Obstetrics and Gynecology 2012;165(2):156-164.

Morris EP, Rymer J, Robinson J, Fogelman I. Efficacy of tibolone as add-back therapy' in conjunction with a gonadotropin-releasing hormone analogue in the treatment of uterine fibroids. Fertility and Sterility 2008;89(2):421-428.

Simpson PD, McLaren JS, Rymer J, Morris EP. Minimising menopausal side effects whilst treating endometriosis and fibroids. Post Reproductive Health: The Journal of the British Menopause Society. 2015;21(1):16-23.

Stewart EA. Clinical Practice. Uterine Fibroids. N Engl J Med. 2015;372(17):1646-55.

Wu D, Hu M, Hong L, Hong S, Ding W, Min J, Fang G, Guo W. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. Archives of Gynecology and Obstetrics 2014;290(3):513-523.

Zupi E, Marconi D, Sbracia M, Zullo F, De Vivo B, Exacustos C, Sorrenti G. Add-back therapy in the treatment of endometriosis-associated pain. Fertility and Sterility 2004;82(5):1303-1308.

Myovant Sciences GmbH 84 CONFIDENTIAL

APPENDICES

Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

Myovant Sciences GmbH 85 CONFIDENTIAL

Appendix 2. Daily eDiary

Clinical Study Medication

1. Did you take your dose of study treatment **today**?

   □ Yes

   If Yes, please provide

   Date: dd – MMM - yyyy

   Time: HH:MM [AM/PM]

   □ No

2. Did you take your dose of study treatment while **on an empty stomach**? (i.e., at least 1 hour before a meal)

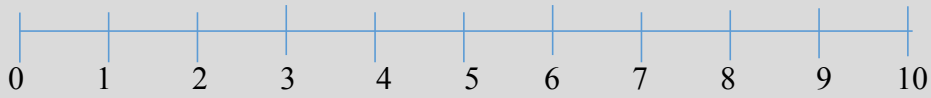
   □ Yes

   □ No

   □ Not applicable, I did not take a dose today

Uterine Fibroid Pain

Please rate your pain caused by your uterine fibroids by indicating the number that best describes your pain at its worst in the last 24 hours:



No Pain Pain As Bad As You Can Imagine

Menstrual Bleeding

1. Did you experience any menstrual bleeding **today**?

   □ Yes (this includes spotting as well as bleeding)

   □ No

2. Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?

   □ Yes

   □ No

Myovant Sciences GmbH 86 CONFIDENTIAL

Use of Pain Medication (Analgesics) and Supplements

1. Did you take any medication **today** to treat pain caused by your uterine fibroids?

   □ Yes

   If yes, record medication:_____

   □ No

Myovant Sciences GmbH 87 CONFIDENTIAL

Appendix 3. Menorrhgia Impact Questionnaire

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

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

MIQ, Menorrhagia Impact Questionnaire.

Appendix 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?	□	□	□	□	□

	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 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 ❑

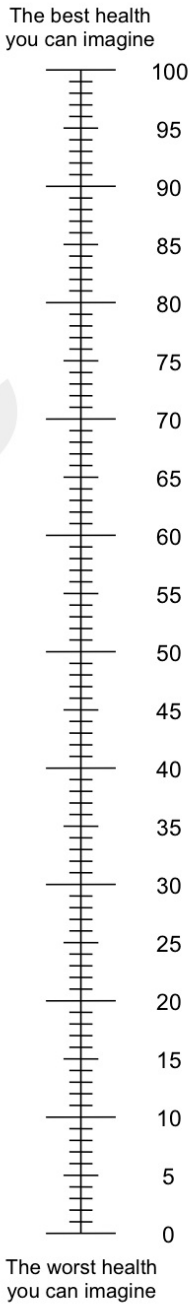
ANXIETY / DEPRESSION

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 ❑

2

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

YOUR HEALTH TODAY = ☐



Appendix 6. 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

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

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- CBC with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.;
- Serology for celiac disease;
- Appropriate liver imaging;
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

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

AMENDMENT 2: SUMMARY OF CHANGES

Protocol MVT-601-3002 entitled "LIBERTY 2: 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" has been amended as described in the table below. The main purpose of the amendment was to provide clarification regarding roll-over of patients into the extension study MVT-601-3003 and follow-up assessments for patients who do not enroll in the extension study. Modifications were also made to the secondary efficacy endpoints related to disease related symptoms and impact of disease on activities, function and quality of life. This includes the addition of a new patient global assessments for function and symptoms. The amendment also includes modifications or clarifications to study eligibility as well as study procedures or tests. A detailed list of changes is described below. Note that corrections of typos, minor clarifications and minor wording changes to improve readability and understanding are not included in this table.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Synopsis: Location	Multinational, including North and South America, Europe, and Australia	Multinational, including North and South America, **South Africa, and** Europe ~~**and Australia**~~	To update regions where study is conducted.
Title Page: Sponsor	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland	Myovant Sciences GmbH **Viaduktstrasse 8** **4051** Basel Switzerland	Sponsor address updated.
Synopsis: Secondary Efficacy Objectives Section 3 Study Objective and Endpoints	• 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: … None. None.	• 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 Impact of uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient	To add a new secondary efficacy objective related to the impact of uterine fibroids on symptoms, activities, and QOL and to add a patient global assessment for function and symptoms. Clarified the instrument to be used for assessing impact of heavy menstrual bleeding on social, leisure and physical activities.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		Global Assessment (PGA) for function and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities **as measured by the Menorrhagia Impact Questionnaire (MIQ)**; o **Pain associated with uterine fibroids;**	
Synopsis: Safety Objectives Section 3 Study Objective and Endpoints	None. None.	• To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • To determine the incidence of vasomotor symptoms with 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.	Objectives related to BMD analysis at 12 weeks and analysis of vasomotor symptoms are added
Synopsis: Study Design Section 4.1 Overall Study Design Section 5.1 Treatments Administered	During the randomized treatment period, study participants will take blinded study treatment orally once daily for 24 weeks.	During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. **The last dose of study drug for the Randomized Treatment Period will be taken on the immediate day prior to the Week 24 visit.**	To allow transition into the extension study (MVT-601-3003). Week 24 visit will be the first day of MVT-601-3003. Patients who qualify for and provide informed consent to enroll in MVT-601-3003 will take the first dose of open label study drug at Week 24.
Synopsis: Study Design	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	During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken	Added additional text to provide details on the transition of patients into the extension study (MVT601-3003). The Week 24 visit will be the

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	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).	on the day immediately before to the Week 24 visit. Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where 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 patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).	first day of the extension study. Also added additional follow-up activities for patients not enrolling into the extension study.
Synopsis: Inclusion Criteria Section 4.3.1 Inclusion Criteria Section 4.7 Contraception/ Pregnancy Avoidance	8. Agrees to use two forms of nonhormonal contraception (dual contraception, as described in Section 4.7) consistently during the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she: …	8. Agrees to use ~~**two forms of nonhormonal**~~ contraception **during the study and for 30 days following the last dose of study drug. Specifically agrees to use** nonhormonal contraception, ~~**(dual contraception**~~ as described in Section 4.7 consistently during the Screening period, and the Randomized Treatment Period **and either nonhormonal or oral contraceptives after return of**	To specify use of contraceptives for 30 days following treatment. Also removed the requirement for dual nonhormonal contraception as spermicide is not available in all countries.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;	**menses following treatment discontinuation.** However, the patient is not required to use ~~**dual**~~ **specified non-hormonal** contraception if she: … c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of ~~**dual**~~ non-hormonal contraception **as described in Section 4.7**;	
Synopsis: Inclusion Criteria Section 4.3.1 Inclusion Criteria	9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;	9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: ~~**polyps < 2.0 cm by ultrasound are not excluded;**~~ **Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or <2 cm are eligible;**	To provide clarity.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	4. Has a weight that exceeds the weight limit of the DXA scanner;	4. Has a weight that exceeds the weight limit of the DXA scanner **or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);**	Adds exclusion for any other condition that would interfere with obtaining an interpretable DXA scan.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	6. … A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;	6. … ~~**A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;**~~ **Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;**	To provide clarity.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	13. Has any of the following clinical laboratory abnormalities at any screening visit: … … d. None. e. None.	13. Has any of the following clinical laboratory abnormalities at any screening visit: … d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN); e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN)	Added to exclude patients with conditions that would result in abnormal calcium and phosphorus levels.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	14. Has clinically significant cardiovascular disease including: … e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec; g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;	14. Has clinically significant cardiovascular disease including: … e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec **on the Screening visit or Baseline Day 1 ECG;** g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg ~~**on 2 repeat measures at least 15 minutes apart**~~ or diastolic blood pressure > 100 mmHg **on 2 repeat measures at least 15 minutes apart** at any screening visit or the Baseline Day 1 visit;	To provide clarification on visits for the exclusion criteria. To clarify that both systolic and diastolic blood pressure criteria must be demonstrated on 2 repeat measures.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	16. Has a history of clinically significant condition(s) including, but not limited to the following: … a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded); None.	16. Has a history of clinically significant condition(s) including, but not limited to the following: … a. Untreated thyroid dysfunction ~~**or palpable thyroid abnormality**~~ (patients with adequately treated hypothyroidism who are stable on medication are not excluded); d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;	Deleted as redundant. Untreated palpable abnormality would generally fall under untreated thyroid dysfunction. To add an exclusion criterion for systemic autoimmune disease.
Synopsis:	17. Is currently pregnant or	17. Is currently pregnant or	To clarify the

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Exclusion Criteria Section 4.3.2 Exclusion Criteria	lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;	lactating, or intends to become pregnant **during the study period through 1 month after the last dose of study drug** or **intends** to donate ova during the study period or within 2 months after the last dose of study drug;	pregnancy window.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.	23. Is inappropriate for participation in this study ~~**for other reasons**~~ **because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements,**-as determined by the investigator, sub-investigator, or medical monitor;	To explain circumstances and provide examples when a potential patient would be inappropriate for participation in the study.
Synopsis: Exclusion Criteria Section 4.3.2 Exclusion Criteria	None.	24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.	Added new exclusion criteria to avoid confounding the assessment of hemoglobin.
Synopsis: Secondary Efficacy Endpoints Section 3 Study Objective and Endpoints Section 9.3.2 Statistical Considerations and Data Analyses	The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: … • Proportion of women who achieve amenorrhea over the last 35days of treatment as measured by the alkaline hematin method; • Time to amenorrhea as measured by the by the alkaline hematin method; None. None.	The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: … • Proportion of women who achieve amenorrhea over the last 35 days of treatment ~~**as measured by the alkaline hematin method;**~~ • None. • Change from Baseline to Week 24 in impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11;	Time to amenorrhea Endpoint removed due to redundancy. Presenting the amenorrhea rate using a proportion versus a cumulative Kaplan-Meier probability is preferred since it is more consistent with method used for the primary responder endpoint analysis. Added secondary endpoints related to UFS-QOL and PGA for function and symptoms to address the added secondary objectives.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	None. None. None. None. None. None.	• Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to Week 24;	
Synopsis: Safety Endpoints Section 3 Study Objective and Endpoints	None. • 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;	• Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week~~s~~ **~~12 and~~** 24 in bone mineral density at the **lumbar** spine (~~average of~~ L1-L4), total hip, and femoral neck as assessed by DXA;	Endpoint for assessment of bone mineral density at Week 12 is pre-specified as a separate endpoint with comparison between Group A and Group B. This endpoint will support inclusion of add-back therapy in the treatment regimen.
Synopsis: Exploratory Endpoints Section 3 Study Objective and Endpoints Section 9.6 Exploratory Analyses	• 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;	None.	Exploratory endpoints related to UFS-QOL are removed, and secondary endpoints related to assessments of certain components UFS-QOL are added.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 1.1 Schedule of Activities Table 1-1	Visit window timing (days) Week 24 (or Early Termination of Study Drug) ± 10 None. Treatment Compliance Week 4 through Week 24 None. Week 24 (or Early Termination of Study Drug) None. Follow-up None.	Visit window timing (days) Week 24 (or Early Termination of Study Drug): ~~± 10~~ **-10/+20** PGA for function PGA for symptoms Treatment Compliance **and Study Drug Accountability** Week 4 through Week 24 Treatment compliance and drug accountability Week 24 (or Early Termination of Study Drug) Urinalysis Follow-up Temperature collection, pregnancy test, status of menstruation recovery	Visit window expanded to allow transition of eligible patients into open label extension study MVT-601-3003 without interruption. Added new assessments in line with new secondary efficacy endpoints. Updated to clarify the assessment. Added additional assessments for treatment compliance and urinalysis at week 24. Added additional assessments for follow up visit for patients who do not roll-over to the extension study.
Section 1.1 Schedule of Activities Table 1-1 footnotes	d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose pharmacodynamic 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 other study procedures and prior to first dose of study drug.	d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. **The following procedures must be completed prior to randomization: urine pregnancy, vital signs, waist circumference, weight, temperature, complete physical examination, visual acuity assessment,12-lead ECG, and review of eligibility criteria.** Collect clinical laboratory **sample**, PK sample**,** ~~**pre-dose**~~ pharmacodynamic sample, ~~**pregnancy**~~ and urinalysis prior to first dose of study drug. ~~**The patient must**~~ **Whenever possible,** complete MIQ, UFS-QOL, **PGA for symptoms and PGA for function,** and EQ-5D-	To clarify order of assessments during baseline Day 1 visit.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		5L ~~questionnaires prior other study procedures and~~ prior to the first dose of study drug.	
	e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.	e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit. **The last dose of study drug in the Randomized Treatment Period will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.**	To provide clarity on definition of Week 24 visit and when the last dose is taken.
	h. Visual acuity must be assessed with the study eye chart. The patient should wear any prescription glasses or contacts during the assessment.	h. Presenting visual acuity must be assessed with the supplied study eye chart. **If the** patient **uses corrective lenses, she** should wear **~~any~~her usual** prescription glasses **or contact lenses** during the assessment, **and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions. See Study Reference Manual for additional instructions on visual acuity testing and see Section 6.8.2.8 for overall guidance including follow-up.**	To provide guidance on visual acuity examination and follow-up.
Section 1.1 Schedule of Activities Table 1-1 footnote i Section 6.2.1 Screening 1 Visit Section 6.8.2.3 Physical and Gynecologic Exams	Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit.	Papanicolaou test must be conducted for women without a test result within **~~6 months~~ 2 years** prior to the Screening 1 visit.	Window for Papanicolaou test expanded to approach the guidelines for cervical cancer screening.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 1.1 Schedule of Activities Table 1-1 footnote j	…Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests.	…Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests. **In addition to clinical chemistries and a complete blood count, include thyroid-stimulating hormone at Screening 1. Screening laboratory tests may be repeated during the screening period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor. 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 reported through the central lab.**	To provide clarification on laboratory tests: to indicate thyroid-stimulating hormone testing at Screening 1, repeats of screening tests, and testing for iron and ferritin in patients with microcytic anemia.
Section 1.1 Schedule of Activities Table 1-1 footnote k	…In addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, Vitamin D, iron, ferritin, and hemoglobin A1c.	…In addition to clinical chemistries and a complete blood count, include a lipid profile, ~~**levels of parathyroid hormone, thyroid-stimulating hormone,**~~ prolactin, Vitamin D, ~~**iron, ferritin,**~~ and hemoglobin A1c.	Parathyroid hormone testing is removed (patients with abnormal calcium and phosphorus will be excluded). Thyroid stimulating hormone level will be obtained at Screening 1.
Section 1.1 Schedule of Activities Table 1-1 footnotes m, n	…Administer study drug after PK and pharmacodynamics sample collections are complete…	…Administer study drug after PK and pharmacodynamics sample collections are complete **(Study drug is not administered at Week 24 Visit; for patients proceeding into the extension study, refer to protocol for study MVT-601-3003).**	Added note at end of footnotes for PK and PK samples clarifying that no study drug is administered at the Week 24 visit
Section 1.1 Schedule of Activities Table 1-1 footnote o Section 6.8.1.11 Pharmacogenomics Sample	Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected.	Pharmacogenomics sample **(unless precluded by local law or regulations)**: a separate pharmacogenomics consent is required before this sample may be collected.	Added note that pharmacogenomics sample will not be obtained if precluded by local laws or regulations

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Collection			
Section 1.1 Schedule of Activities Table 1-1 footnotes	None.	w. Patients not proceeding to the extension study who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will be followed and will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination visit (see Section 6.7). The repeat biopsy will be submitted to the central laboratory.	Added new footnote to provide guidance on scheduling DXA assessments and follow-up for patients not entering the extension study.
	None.	x. Schedule DXA as early as possible within the Week 24/Early Termination visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo another DXA scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.	Added new footnote for follow-up procedures for abnormal endometrial biopsy for patients not proceeding into the extension.
	None.	y. Patient will enter responses in a paper questionnaire at the site.	Added new footnote that PGAs for functions and symptoms are completed as a paper questionnaire.
	None.	z. The patient should be asked to bring all study drug to the clinic at each visit. Please refer to section 5.8.	Clarification.
Section 2.2.4.4 Clinical Studies in Women with Uterine Fibroids or	The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to	Adverse drug reactions associated with relugolix in women with uterine fibroids or endometriosis include hot flush, headache, hyperhidrosis and bone	Updated for consistency with the Investigator Brochure.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Endometriosis and Men with Prostate Cancer	relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.	density decreased. Adverse drug reactions associated with relugolix in men with prostate cancer include hot flush, fatigue, arthralgia, nausea, weight increased, gynecomastia and night sweats.	
Section 4.1 Overall Study Design Figure 4-1	Open-Label Extension Study (Eligible Patients) 24 Weeks	Open-Label Extension Study (Eligible Patients) **28** Weeks	Study schematic updated to indicate the open-label extension is 28 weeks instead of 24 weeks
Section 4.1 Overall Study Design Figure 4-2 Figure legend	Bottom scenario: … • Patients whose first screening cycle MBL is < 80 mL and whose second screening cycle menstrual blood loss is > 160 mL will follow the bottom scenario visit schedule Additional Scenarios (not depicted): … • … If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule.	Bottom scenario: … None. Additional Scenarios (not depicted): … • … If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule, **and the patient does not need to collect menstrual blood loss for another cycle.**	Clarification Schematic of Screening Visit Scenarios is updated to indicate that for patient with MBL ≥ 160 mL do not need to collect menstrual blood loss for another cycle.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 4.6 Removal of Patients from Therapy	• Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements.	• Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements. **This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days of eDiary completion;** • **Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;**	To provide definition of gross non-compliance. Add criteria for withdrawal from treatment for patient whose treatment assignment has been unblinded to harmonize with Section 5.7.
Section 4.7 Contraception/ Pregnancy Avoidance	In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply: … The only acceptable methods of dual contraception are: • Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);	In this study, medications and devices containing hormones **for contraception** are excluded, and patients must agree to use ~~**two forms of**~~non-hormonal contraception ~~**(dual contraception)**~~ **throughout the study, including through 30 days following the last dose of study drug**, unless any of the following apply: … The only acceptable methods of ~~**dual**~~ contraception **for those for whom one of the above methods do not apply** are: • Condom **(male or female condom)** with **or without** spermicide (cream, spray, foam, gel, suppository or polymer film);	As the common spermicide, nonoxynol-9 (N-9), is no longer approved in several countries participating in the study and other effective spermicides are not readily available in those countries, the protocol-specified contraceptive methods were reviewed and the use of a condom (male or female) with or without spermicide permitted.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 5.1 Treatments Administered	Each patient will be instructed to take one tablet and one capsule per day.	Each patient will be instructed to take one tablet and one capsule per day. **The last dose of study drug will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.**	Added text to clarify last dose due to transition into extension study (see above).
Section 5.4 Directions for Administration	The study treatment should be taken in the fasted state (other than water) in the morning, at least 1 hour before breakfast. … Patients should take any oral iron supplementation with meals.	The study treatment should be taken in the fasted state (other than water**, tea, or coffee**) in the morning, at least 1 hour before breakfast. … None.	Definition of fasted state for drug administration is clarified to include tea or coffee. Restriction to take iron with meals is removed.
Section 5.5 Dose Reduction/Dose Administration Section 7.1.1 Adverse Event	…Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).	**~~…Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event.~~** Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).	Text removed as it is the investigator's responsibility to determine appropriate management of study drug in a setting of an adverse event
Section 5.6 Storage, Packaging, and Labeling	Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 35°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee).	Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to **~~35°C~~ 25°C** with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). **Study drug should be stored protected from light.**	Modified to be consistent with study drug labeling.
Section 5.7 Blinding	Investigators will have direct access to a given patient's individual study treatment, however, the investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options **before** unblinding the patient's treatment assignment.	**~~Investigators will have~~The decision to unblind a patient's treatment assignment in an emergency situation resides with the investigator who has** direct access to **unblind** a patient's individual study treatment; however, the investigator should **~~make every effort~~**attempt to contact the medical monitor or appropriate study personnel to discuss	To provide clarification that the decision to break the treatment code in emergency situation resides with the investigator.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		options before unblinding the patient's treatment assignment **unless the urgency of the medical situation precludes this.**	
Section 5.8 Study Drug Accountability and Treatment Compliance	If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%) it may be appropriate to withdraw the patient from the study.	If a patient is persistently noncompliant with the study treatment **~~(ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%)~~** it may be appropriate to withdraw the patient from the study **(see Section 4.6).**	Revised to align with criteria for removal from therapy.
Section 5.10.1 Prohibited Medications Table 5-3	Anti-convulsant drugs (specified) Examples phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	Anti-convulsant drugs (specified) Examples phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone **Note: All other anticonvulsants are allowed**	Added clarification that other anticonvulsants not listed are allowed.
	Progestins Examples dienogest norethindrone medroxyprogesterone	Progestins **and progestin implants.** Examples dienogest norethindrone medroxyprogesterone **cyproterone** **etonogestrel**	To include additional examples of prohibited medications.
	Estrogen Examples estradiol valerate conjugated estrogens	Estrogen Examples estradiol valerate conjugated estrogens **ethinyl estradiol**	To include additional examples of prohibited medications.
	Oral Contraceptives Examples combined or progestin only	**Hormonal ~~oral~~ contraceptive patches and vaginal rings** Examples combined or progestin only **Nuva Ring**	To include additional examples of prohibited medications.
Section 5.10.1 Prohibited Medications	Bone Agents Window/Comments No prior use if used for reduced	Bone Agents Window/Comments No prior use if used for reduced	Provide a specific clarification that Calcium and vitamin

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Table 5-3	bone mineral density	bone mineral density **Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.**	D are allowed.
Section 5.10.1 Prohibited Medications Table 5-3	P-glycoprotein Inducers Examples carbamazepine rifampin St. John's wort	P-glycoprotein Inducers Examples **avasimibe** carbamazepine **phenytoin** rifampin St. John's wort **tipranavir/ritonavir**	To include additional examples of prohibited medications. Clarify when short term use of these Pgp inducers can be allowed in study.
Section 5.10.1 Prohibited Medications Table 5-3	Moderate and Strong P glycoprotein Inhibitors Examples None. Footnotes None.	Moderate and Strong P glycoprotein Inhibitors Examples amiodarone, atazanavir[f], azithromycin[a], captopril[b], carvedilol[g], clarithromycin[a], cobicistat[f], conivaptan, cyclosporin[c], diltiazem, dronedarone, erythromycin[a], felodipine[d], itraconazole[e], ketoconazole[e], lopinavir/ritonavir[f], quercetin, quinidine,,ranolazine, ticagrelort[g], verapamil Footnotes **a. Roxithromycin is allowed** **b. All other angiotensin converting enzyme inhibitors are allowed** **c. Tacrolimus is allowed** **d. Amlodipine and nifedipine are allowed** **e. Fluconazole is allowed** **f. Integrase inhibitors are allowed** **g. Metoprolol and atenolol are permitted**	To include additional examples of prohibited medications. Clarify when short term use of these Pgp inhibitors can be allowed in study.
Section 6.2.1 Screening Visit 1	The order of procedures should be as follows. …	The order of procedures should be as follows. …	Added new text to provide clarification

Item; Section(s)	Amendment 1	Amendment 2	Rationale
	None. None.	• Complete physical examination and visual acuity assessment • Clinical laboratory tests, including TSH, urinalysis	for the order of procedures.
Section 5.10.2.2 Iron Therapy Section 6.2.1 Screening Visit 1 Section 6.2.2 Screening Visit 2 Section 6.8.2.4 Clinical Laboratory Samples	None. 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	**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 reported through the central lab.** 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 **reported through the central lab ~~obtained as an unscheduled test~~.**	Added new text to provide guidance on laboratory diagnosis and management of iron deficiency anemia. For Section 6.2.2 Clarified that iron and ferritin are be reflex labs that will be reported trough central laboratory.
Section 6.2.6 Retesting	None.	Screening laboratory tests may be repeated once during the Screening period, if necessary, at the investigator's discretion. For laboratory-based entry criteria, the most recent value will be used to determine eligibility. Additional laboratory retesting requires the approval of the medical monitor. Retesting of other procedures (except once, as required, due to technical or logistical issues such as an inadequate sample) also require approval of the medical monitor.	New section added to allow single repeat of screening laboratory tests.
Section 6.6 Additional Safety Follow-Up Procedures	None.	For patients not continuing into the extension study (MVT 601-3003), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits. • 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	New section added to provide guidance for additional safety follow up procedures for patients who do not proceed into extension study.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		has resumed and questioned about factors that may affect resumption of menses. • Patients with endometrial biopsy findings of endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings during through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory. In addition, patients with endometrial hyperplasia with atypia will be evaluated and managed, as needed, by a gynecologist. • Patients who have had a bone mineral density loss of > 2% at the lumbar spine (average of L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scanning. The follow-up DXA scan will be submitted for central reading.	
Section 6.8.1.2 Transvaginal and Transabdominal Ultrasound	None.	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	Added clarification regarding use of saline or gel contrast for ultrasound.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		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	
Section 6.8.1.5 Patient Diary	The eDiary data will be reviewed by the investigator to identify any potential adverse events.	The eDiary data will be reviewed by the **study staff.** ~~**investigator to identify any potential adverse events**~~	To ensure consistency with section 7.2 of the protocol stating that eDiary entries will be reviewed by study site personnel.
Section 6.8.1.9 Patient Global Assessment for Symptoms and Patient Global Assessment for Function	None.	These simple questions are used by the patient to qualitatively describe severity of symptoms or effects on function (PGA) (see Appendix 6) on a schedule described in the Schedule of Activities (Section 1.1). With the exception of Baseline Day 1 (see Section 1.1), patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (Section 1.1). With the exception of Baseline Day 1, patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site.	New section added to describe assessments for the newly add PGA secondary objectives.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Section 6.8.1.10 Status of Menstruation Recovery	After the Follow-up visit, additional follow-up for the status of menstruation recovery will not be continued.	None.	Menstruation recovery follow up outlined in Section 6.6.
Section 6.8.2.3 Physical and Gynecologic Exams	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.	None.	Visual acuity assessment instructions moved to a new section.
Section 6.8.2.4 Clinical Laboratory Samples **Table 6-1**	Chemistry Creatinine Kinase Hormones Intact Parathyroid Hormone	Chemistry ~~**Creatinine Kinase**~~ Hormones ~~**Intact Parathyroid Hormone**~~	Parathyroid hormone testing is removed (patients with abnormal calcium and phosphorus will be excluded). "Creatinine kinase" Typographical error removed.
Section 6.8.2.6 Endometrial Biopsy	An endometrial biopsy is to be performed during the pelvic examination at the Screening 3 visit. A pipelle should be used to obtain the specimen. A second biopsy is to be performed at the Week 24 visit. The biopsies will be read centrally.	An endometrial biopsy will be obtained using an endometrial suction curette (eg, Pipelle®) and submitted to the central laboratory for reading. If the biopsy is inadequate for diagnosis at either Screening or at Week 24, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate for diagnosis at Screening, the patient is not eligible for the study. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound).	To provide clarification and details for endometrial biopsy.
Section 6.8.2.7 Bone Mineral Density	Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient.	Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient). **The scans will be read by the central radiology laboratory in**	Added clarification of central reading.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		accordance with the imaging charter.	
Section 6.8.2.7 Bone Mineral Density	The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): 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, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.	None.	Deleted details on analysis of bone mineral density. This info will be provided in the SAP.
Section 6.8.2.7 Bone Mineral Density	Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the sties assessed during the study. In this case, repeat scan may be required for confirmation of the results, and it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.	Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the **anatomical** sites assessed during the study. In this case, ~~**repeat scan may be required for confirmation of the results, and**~~ **it is at the investigator's discretion to consider the patient's status and determine future management.** Detailed instructions for ~~**bone mineral density monitoring**~~ ~~**DXA scanning**~~ will be provided in the Study Reference Manual. **Please see Section 6.6 for follow-up of patients who are not continuing into the extension study (MVT-601-3003) and whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit relative to Baseline.**	Further specified follow-up measures for observed bone mineral density loss.
Section 6.8.2.8 Visual Acuity	None.	Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual	New section created to provide additional details and to align with other studies with relugolix.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details). Patients whose presenting visual acuity score is 90 or lower at the Baseline visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history. Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from Baseline should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.	
Section 7.1.1 Adverse Event	Events that do not meet the definition of an adverse event include: … • None.	Events that do not meet the definition of an adverse event include: … • Events of heavy menstrual bleeding, as heavy menstrual bleeding is quantified as an efficacy endpoint, unless the event meets seriousness criteria.	As heavy menstrual bleeding is being assessed as an efficacy endpoint, added it to list of events that do not meet definition of adverse event. Also clarified that would be reportable as an adverse event if met the criteria for seriousness.
Section 7.6 Serious Adverse Event Reporting	Table providing details to send completed Safety Report Forms to PRA Safety & Risk Management	Table updated to send completed Safety Report Forms to **QuintilesIMS**	Updated Contact info for reporting Serious Adverse events. Updates to e-mail and phone number are also included in this section.
Section 7.10 Benefit/Risk Assessment	<u>Impact on Eligibility</u> Exclusion criteria for a history of osteoporosis, osteopenia,	<u>Impact on Eligibility</u> Exclusion criteria for a history of osteoporosis, ~~**osteopenia**~~ ,	Osteopenia is not an exclusion criterion in this study.

Item; Section(s)	Amendment 1	Amendment 2	Rationale
Table 7-2	metabolic bone disease, …	metabolic bone disease, …	
Section 7.10 Benefit/Risk Assessment Table 7-2	Hepatic Enzymes	Hepatic Enzyme **Increase**	Updated naming of this potential risk, matching IB nomenclature
Section 9.2 Statistical Considerations and Data Analyses	The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations.	The Per-Protocol Population will consist of those members of the ITT Population who have no **relevant** major protocol violations, **defined as a subset of all major protocol violations (details will be provided in the statistical analysis plan).**	Clarification.
Section 9.3.2 Statistical Considerations and Data Analyses	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 for whom the first time at which menstrual blood loss of <80 mL AND at least a 50% reduction from baseline is achieved is during a cycle when no feminine products were returned due to amenorrhea absence of a menstrual period, the most recent menstruation stop date will be used. … Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline.	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 for whom the first time at which menstrual blood loss of <80 mL AND at least a 50% reduction from baseline is achieved is during a cycle when no feminine products were returned due to amenorrhea absence of a menstrual period, the most recent menstruation stop date will be used.**~~ … Descriptive statistics will be provided for changes in menstrual blood loss, hemoglobin, **UFS-QOL score, PGA for function and symptoms, MIQ Score,** Numerical Rating Scale score for uterine fibroid-associated pain, uterine volume, and uterine fibroid volume baseline.	Changes made to ensure consistency with changes in secondary efficacy endpoints.
Section 9.4 Safety Analyses	None.	To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of	To provide clarification on analysis plans for

Item; Section(s)	Amendment 1	Amendment 2	Rationale
		mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal comparison of Group A versus Group B (see details in the joint statistical analysis plan).	bone mineral density which includes pooling of data across the two replicate studies.
Appendix 6 Patient Global Assessments	None.	Patient Global Assessment (for function) How much were your usual activities limited by uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? 1. No limitation at all 2. Mild limitation 3. Moderate limitation 4. Quite a bit of limitation 5. Extreme limitation Patient Global Assessment (for symptoms) How severe were your uterine fibroids symptoms such as heavy bleeding over the last 4 weeks? 1. Not severe 2. Mildly severe 3. Moderately severe 4. Very severe 5. Extremely severe	To support secondary objectives.

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 2: 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
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 10-FEB-2017

SPONSOR SIGNATURE PAGE

LIBERTY 2: 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-601-3002

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

PPD

13Feb2017
Date

13-Feb-2017
Date

13-Feb-2017
Date

AMENDMENT 1: SUMMARY OF CHANGES

Item; Section(s)	Original	Amendment 1	Rationale
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	LIBERTY 2: 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	To add the study moniker
Sponsor Signature Page		Biostatistics and Medical Director signatories added; CEO signatory removed	To update signatories based on personnel additions
Study Schematic 4.1		Updated Figure 4-1	To indicate procedures consistent with the SOA
IC #3; Synopsis, 4.3.1	"Has a body mass index (BMI) within the range of 18.0 to 40.0 kg/m^2 (inclusive);"	None	Weight restriction, other than as related to DXA scanner accommodation (covered in EC #4) was not needed.
IC #5 (now IC #4); Synopsis, 4.1, 4.3.1, 6.2, 6.3, SOA footnote q	"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"	"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	To clarify situations in which a transabdominal ultrasound and saline or gel infusion should be performed

Item; Section(s)	Original	Amendment 1	Rationale
		required, but may be performed to demonstrate fibroids that meet the criterion for inclusion if these are not adequately visualized with transvaginal ultrasound alone."	
EC #5; Synopsis, 4.3.2	Has a baseline bone mineral density z-score < -2.0 at spine or total hip	Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck	To exclude patients with baseline bone mineral density z-score of < -2.0 at femoral neck
Placebo Matching; Synopsis, 5.1	Placebo and active tablets and capsules will matched for size, shape, color, and odor	Placebo and active tablets and capsules will matched for size, shape, and color	Odor is not being specifically tested.
IC #4 (now IC #5); Synopsis, 4.1, 4.2, 4.3, 4.3.1, Figure 4-1, Figure 4-2	"Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 80 mL per cycle as measured by the alkaline hematin method for 2 menstrual cycles during the screening period"	"Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss of ≥ 160 mL for 1 cycle or ≥ 80 mL per cycle for 2 menstrual cycles as measured by the alkaline hematin method during the screening period"	To allow patients who have demonstrated menstrual blood loss that is double or more the screening requirement in a single cycle to enroll based on menstrual blood loss data from only one cycle, rather than two
IC #7 (now IC #6); Synopsis, 4.1, 4.3.1	"…not expected to be a candidate for gynecological surgery or ablation procedures…"	"…not expected to undergo gynecological surgery or ablation procedures for uterine fibroids…"	To clarify the criterion's intent
IC #9 (now IC #8); Synopsis, 4.1, 4.3.1, 4.7	"Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram"	"Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure™ syndrome" in the investigator's opinion)"	To exclude women with the potential confounding factor of post-Essure syndrome

Item; Section(s)	Original	Amendment 1	Rationale
IC #10 (now IC #9); Synopsis, 4.1, 4.3.1	"Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, endometritis, or endometrial cancer)"	"Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded."	To remove endometritis as an exclusion and to make polyp exclusion consistent with other entry criteria
IC #11 (now IC #10); Synopsis, SOA footnote p, 4.1, 4.3.1, 6.2.1, 6.2.2	"If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 3 or equivalent) during the screening period or within 3 months prior to the screening period."	"If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period."	To align with recommended mammography screening intervals, accounting for an ~6-month Treatment Period; Disallow patients with BI-RADS 3 readings due to their higher risk
IC #12; Synopsis, 4.3.1	A randomization authorization form has been signed by a study medical monitor approving the patient for randomization into the trial.	None	To define the use of randomization authorization in the study procedural documents rather than in the protocol

Item; Section(s)	Original	Amendment 1	Rationale
EC #1; Synopsis, 4.1, 4.3.2, 6.2, SOA footnote q	"Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment."	"Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥2.0 cm, large simple ovarian cyst >4.0 cm, endometrioma(s) >4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study. Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal or transabdominal ultrasound (e.g., suspected intrauterine masses, equivocal endometrial findings, etc.)."	To add examples of common findings that would be considered exclusionary; To clarify situations in which saline or gel infusion should be performed; To allow patients with finding not requiring immediate evaluation or treatment to enroll
EC #2; Synopsis, 4.3.2	"Has unexplained vaginal bleeding outside of the patient's regular menstrual cycle"	"Has known rapidly enlarging uterine fibroids in the opinion of the investigator"	To remove an exclusion that may be a disease-state manifestation and to add an exclusion for uterine fibroids at higher risk to be malignant
EC #10g, h; Synopsis, 4.3.2	none	"Migraine with aura" "History of porphyria"	To add migraine with aura as an example of a contraindication to treatment with low-dose estradiol and norethindrone acetate and to add an exclusion for porphyria, which is listed in the prescribing information in some countries

Item; Section(s)	Original	Amendment 1	Rationale
EC #12; Synopsis, 4.3.2	"Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study."	"Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative."	To incorporate high-risk human papilloma virus reflexive testing that will be performed by the central laboratory into the criterion
EC #14b, d, h; Synopsis, 4.3.2	"History of angina" "History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or history of permanent pacemaker, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute)" "Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram"	"History of angina or significant coronary artery disease (i.e. ≥50% stenosis)" "History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute)" Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness"	To add an exclusion for significant coronary artery disease (#14b), to remove the exclusion for pacemaker (criterion was internally inconsistent) (#14d), and to allow for physiologically appropriate bradycardia in physically-fit patients (#14h)

Item; Section(s)	Original	Amendment 1	Rationale
EC #16c; Synopsis, 4.3.2	"History of major depression or other major psychiatric disorder at any time including bipolar disorder, schizophrenia, or post-traumatic stress disorder (patients without a history of major depression treated with a selective serotonin-reuptake inhibitor antidepressant may be enrolled if stable for over 1 year)"	"Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled."	To broaden the ability for patients with remote psychiatric disorders and current psychiatric disorders who are able to participate in the trial to be enrolled
EC #17; Synopsis, 4.3.2	"Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 1 month after the end of the study"	"Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug"	To clarify timing relative to last dose of study drug
Study Completion; 4.6	None	Added definition of study completion (completion of Week 24 visit)	To include a definition

Item; Section(s)	Original	Amendment 1	Rationale
Removal of Patients from Therapy; 4.6, 6.7.2.6	Patients who have percent change from Baseline in bone mineral density at either the Week 12 or Week 24 visit (or any unscheduled visit) at the lumbar spine (average L1-L4), total hip, or femoral neck of < -4.0 that is repeated and confirmed (ie, both values are < -4.0)	Replaced with alert notifications from the central radiology readers to the investigator for a 7% or greater decline in bone mineral density at any time point (added to section 6.7.2.6)	To allow for use of clinical risk assessment by the investigator in determining whether withdrawal is warranted and determination of future management. The study is conducted in patients generally considered at low risk for fracture; Patients with history of osteoporosis, or baseline bone mineral density Z-scores < -2.0 are excluded.
Identification of Investigational Product; 5.0. Table 5-1	No color listed Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™ or Activelle™).	"Swedish orange" added in the description for the placebo and active low-dose add back capsule Estradiol (1.0 mg) and norethindrone acetate (0.5 mg) is a fixed-dose combination product (Activella™ or Activelle™).	To add product details
Product Characteristics; Section 5.2.1	Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using the United States Pharmacopeia and the National Formulary (USP/NF) excipients.	"Relugolix has no chiral centers. The compound is slightly to partially soluble in acidic solutions but essentially insoluble at neutral pH (pH 7) and above. It is partially soluble in polar organic solvents. The compound is provided as an immediate-release pink tablet using common excipients. Placebo to match relugolix is a pink tablet using common excipients."	To facilitate review of the protocol in European countries, USP language was made more general

Item; Section(s)	Original	Amendment 1	Rationale
Study Drug Storage; 5.6	"Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 1°C to 30°C until it is used or returned to the sponsor (or designee)."	"Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 25°C with excursion to 15°C to 30°C permitted, until it is used or returned to the sponsor (or designee)."	To narrow the storage temperatures for both relugolix/placebo and estradiol/ norethindrone to match the temperature requirements for Activella
Study Drug Administration; 5.4, 6.3	None	Fasting does not require withholding of water. On clinic visit days that are not in the morning, patients should fast for at least 2 hours prior to the visit and for 1 hour taking the study drug.	To provide clarifications on study procedures
Blinding; 5.7	Investigator to determine if treatment assignment of a site-unblinded patient should be revealed to the sponsor. Sponsor may unblind for a serious adverse event.	Investigator not to reveal treatment assignment of a site-unblinded patient to the sponsor. Sponsor unblinding for serious adverse events described in the Safety Management Plan.	To make this decision a sponsor responsibility; To provide details and context for unblinding of serious adverse events by the Sponsor in the Safety Management Plan, rather than in the protocol
Prohibited Medications; 5.10.1	None	Contact the medical monitor for approval and guidance on study drug administration if a short course of a prohibited P-glycoprotein inhibitor or inducer is required during the study	To provide additional guidance for such situations
Prohibited Medications; 5.10.1	None	Addition of bazedoxifene, zoledronic acid, and factor Xa inhibitors to Table 5-3	To include additional examples of prohibited medications
Prohibited Medications; 5.10.1	Oral contraceptive exclusion period 2 months	Oral contraceptive exclusion period typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months	To shorten exclusionary period for patients following resumption of menses

Item; Section(s)	Original	Amendment 1	Rationale
Prohibited Medications; 5.10.1	Selective progesterone receptor modulator exclusion period 2 months	Selective progesterone receptor modulator exclusion period 6 months	To avoid possible confounding related to the endometrial effects of these drugs
Prohibited Medications; 5.10.1	Bone agent exclusion period 2 months prior to Screening	Bone agent exclusion period indefinite if used for low bone mineral density	To make consistent with eligibility criteria
Prohibited Medications; 5.10.1	None	Addition of 1-week exclusionary window for over the counter and herbal products with known hormonal activity	To reduce possible confounding of efficacy and safety due to these products
Analgesic Medications; 5.10.2.1	Specific required medications for uterine fibroid pain and other pain	Requirements changed to recommendations for allowed medications for uterine fibroid pain. Restriction on analgesics for other pain conditions removed.	To liberalize restrictions based on site feedback while encouraging consistency in analgesic use
Adverse Event Reporting Period; 6.2, 7.2.1, SOA footnote f	Non-serious adverse events occurring after signing of the informed consent form and prior to start of study drug should be recorded as medical history	Non-serious adverse events occurring after signing of the informed consent form and prior to start of study drug should be recorded as adverse events rather than medical history if they are considered related to study procedures; otherwise, they should be recorded as medical history.	To capture study procedure-related adverse events as adverse events
Waist Circumference; SOA, 6.3. 6.7.2.1	None	Waist circumference measured at Baseline Day 1	To obtain data to characterize patients with metabolic syndrome
Ultrasound Procedures; 6.2	None	Addition of clarification that the investigator, rather than the central reader, will determine if any exclusionary pathology is present.	Clarification
Pathology Specimens; SOA footnotes i and r, 6.2, 6.3, 6.7.1.3	Whether the Papanicolaou test and would be locally or centrally read was not specified Endometrial biopsy to be read locally (or centrally read if requested)	Papanicolaou test and endometrial biopsy will be centrally read	To improve consistency of readings and to facilitate site logistics
Unscheduled	None	Reminder add to obtain unscheduled iron studies at Visit 2 if hemoglobin	To improve adherence to the

Item; Section(s)	Original	Amendment 1	Rationale
Iron Studies; 6.2		is ≤ 10 g/dL and mean corpuscular volume is below the lower limit of normal.	protocol requirements
Pre-Screening Procedures; 6.2	Pre-screening procedures	None	To allow sites to utilize site-specific practices for pre-screening
Re-Screening Procedures; 6.2, SOA	None	Certain screening procedures do not need to be repeated for patients who re-screen within 10 weeks of the signing the original informed consent form: transvaginal ultrasound, endometrial biopsy, and bone densitometry.	To reduce patient procedural burden
Early Termination Procedures; 6.5, SOA footnote s	None	Certain early termination visit procedures are not required for patients whose last dose of study drug is during Week 6 or earlier (transvaginal ultrasound, endometrial biopsy, and bone densitometry). These procedures may be done if they will aid in the evaluation of an ongoing adverse event	To reduce patient procedural burden
Unscheduled Visit Procedures; 6.6, SOA	List of procedures to be done to further evaluate adverse events	Adverse events are to be evaluated and concomitant medications, and reason for visit are to be recorded. Other procedures may be done as needed.	Clarification of required and optional procedures at Unscheduled Visits
Clinical Laboratory Tests; 6.7.2.4, Table 6-1, SOA footnote j	Subset of central laboratory tests	All central laboratory tests	To include full list of clinical laboratory tests and to add Vitamin D at Baseline Day 1
Bone Mineral Density; 6.7.2.6	Incomplete details of bone mineral density acquisition and reporting included in this section.	Details of bone mineral density acquisition and reporting moved to the imaging charter.	To have a single document with the full details of this procedure
Endometrial Biopsy 6.7.1.3	None	Specification that a pipelle should be used for the endometrial biopsy	To have greater uniformity in the specimen acquisition
Pregnancy; 7.2		Requirement for reporting partner pregnancies removed	All study patients will be women

Item; Section(s)	Original	Amendment 1	Rationale
Serious Adverse Event Logistics; 7.6	None	Contact information for serious adverse event reporting added	To update with the serious adverse event vendor's logistical details
Safety Analyses; 9.4	The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5% or 6% by body area (lumbar, total hip, and femoral neck) will be estimated with 95% confidence intervals by treatment group. The number and percentage of patients meeting a T-score of < -2.5 by body area will also be estimated with 95% confidence interval by treatment group.	The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar, total hip, or femoral neck) will be estimated with 95% confidence intervals by treatment group.	To align with the statistical analysis plan and remove references to analyses based on cut-offs for T-scores; analyses based on Z-scores will be detailed in the SAP
Schedule of Papanicolaou Testing; SOA	Screening and Week 24/Early Termination	Screening	Procedure not needed because cervical dysplasia not a safety risk in this trial
Schedule of PD Measurements; SOA	Screening 1 visit, Day 1, Weeks 4, 8, 12, 16, 20, 24, and Follow-up	Day 1, Weeks 4, 12, 24, and Follow-up	To remove unneeded sampling time points
Visit Windows; SOA, Figure 4-2, 6.2	Screening 3 visit: Window $\leq$ 10 days after Screening 2 visit Transvaginal ultrasound, gynecology examination, papanicolaou test, endometrial biopsy, mammogram, bone densitometry: Visit 3 Screening 1, 2, and 4 visits to occur within 4 days of end of menses and Baseline Day 1 visit to occur within 4 days of end of menses	Screening 3 visit: Window $\leq$ 15 days after Screening 2 visit. Transvaginal ultrasound, gynecology examination, papanicolaou test, endometrial biopsy, mammogram (schedule appointment), bone densitometry (schedule appointment): Visit 1 Screening 2 and 4 visits to occur within 5(+2) days of end of menses. Screening visit 1 not timed with menses. Screening 4 visit may be skipped if menstrual blood loss with the first cycle collection is $\geq$160 mL.	To improve site logistics and to accommodate turnaround time for patients collecting 1 cycle of menstrual blood loss

Item; Section(s)	Original	Amendment 1	Rationale
Schedule of Visual Acuity Testing and eDiary; SOA footnote u and v, 6.2	Visual acuity at Screening and on Day 1 eDiary: dispense at Screening 3 visit	Visual acuity on Day 1 Paper diary: dispense at Screening 1 visit eDiary: dispense at Screening 1 visit	To remove an unneeded procedure; visual acuity is not an eligibility criterion; therefore, not needed at Screening To allow fuller data capture of menses dates and daily feminine product use
eDiary; Appendix 2	eDiary question text	eDiary screenshots, which also include analgesic medication dose, route, and frequency questions	To update with final e-diary content
UFS-QoL; Appendix 4			To update with correct version of the instrument
CTCAE and IB version; 2.4.2.2 and various	CTCAE, Version 5.0 IB Version 9.0, dated 09 November 2016	CTCAE version not specified in protocol, but the version to be used will be in the study reference manual and noted in the statistical analysis plan.	CTCAE version 5.0 not yet published at the time of study start; IB version removed to avoid discrepancies that may occur when IB is updated during the study
Minor Edits; Various		Corrections of typos, minor clarifications, minor inconsistencies, and minor wording changes	To improve readability and understandability.

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CEO, Chief Executive Officer; CTCAE, Common Terminology Criteria for Adverse Events, DXA, dual x-ray absorptiometry; EC, exclusion criterion; IB, investigator brochure; IC, inclusion criterion; PD, pharmacodynamic; SOA, schedule of activities; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life (Questionnaire)

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 2: 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
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH c/o Vischer AG Aeschenvorstadt 4 CH-4010 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-003727-27 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 10-FEB-2017

SPONSOR SIGNATURE PAGE

LIBERTY 2: 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-601-3002

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

PPD

13Feb2017
Date

13-Feb-2017
Date

13-Feb-2017
Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
EQ-5D	European Quality of Life Five-Dimension Five-Level
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MBL	menstrual blood loss
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menstrual Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart

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

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 2: 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-601-3002
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.

	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. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). 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 will be assessed throughout the study by monitoring adverse events, vital signs, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, 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 Section 4.7) consistently during the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps < 2.0 cm by ultrasound are not excluded;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study.

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the 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.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;

9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, $\geq$ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate $\geq$ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;

g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;

h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;

15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary window periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color.
Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. Primary Efficacy Endpoint • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35days 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. Safety Endpoints • 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. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (Cτ) 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 Endpoints • 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.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women 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 on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the 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, a sample size of 260 (130 patients in each of the relugolix and placebo arms) will provide > 99% power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients

with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3002

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)		Within 5 (+2) days after completion of Screening 1 menses	Within ≤ 15 days after Screening 2 visit	Within 5 (+2) days after completion of 2nd Screening menses	Within 7 days of the start of menses	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 10**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X[e]	X
Waist circumference					X								
Height	X												
Weight	X				X						X	X[e]	X
Temperature	X				X						X	X[e]	
Adverse Event Collection[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[h]					X						X	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Complete Physical excluding GYN Examination	X				X						X		
GYN Examination with Pap Test, if applicable	X[i]												
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X[e]	X
12-Lead Electrocardiogram			X		X			X			X	X[e]	X
Clinical Laboratory Tests[j]	X	X			X[k]	X	X	X	X	X	X[l]	X[e]	X
PK Sample[m]					X	X		X			X	X[e]	
PD Sample[n]					X	X		X			X	X[e]	X
Daily Study Drug Administration					X							X[e]	
Administer Dose of Study Drug in Clinic					X	X	X	X	X	X	X	X[e]	
PGx Sample[o]					X							X[e]	
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X	X[e]	
Urinalysis	X				X							X[e]	
Mammogram[p]	schedule	X											
Transvaginal Ultrasound (with or without Transabdominal Ultrasound)[q]	X										X[s]	X[e]	
Endometrial Biopsy	X[r]										X[r,s]	X[e]	
Bone Densitometry[t]	schedule	X						X			X[s]	X[e]	
Randomization					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X		X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD							SAFETY FOLLOW-UP	
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Dispense Study Treatment					X	X	X	X	X	X		X[e]	
Patient paper diary/ eDiary[u]	X	X	X	X	X	X	X	X	X	X	X	X[e]	
Feminine Product Collection and Venous Blood Sample[v]		X		X		X	X	X	X	X	X	X[e]	
MIQ					X	X	X	X	X	X	X	X[e]	
UFS-QoL					X			X			X	X[e]	
EQ-5D					X						X	X[e]	
Treatment Compliance						X	X	X	X	X	X	X[e]	
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; GYN, gynecology; UFS-QoL, Uterine Fibroid Symptom and Health-Related Quality of Life
For patients who are re-screening, please see Section 6.2.6 for abbreviated screening procedures.

a. The screening period should be initiated after the informed consent form is signed and any exclusionary windows for prohibited medications has been confirmed.
b. Visit to occur within 5 (+2) days of the completion of menses. Visit 4 should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.
c. Visit to occur within ≤ 15 days after Screening 2 visit; eDiary dispensation must occur at least 7 days prior to Baseline Day 1. The alkaline hematin menstrual blood loss collection may be repeated once at the discretion of the investigator if one menstrual cycle does not meet menstrual blood loss criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. Collect clinical laboratory, PK sample, pre-dose pharmacodynamic 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 other study procedures and prior to first dose of study drug.
e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
f. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003) and/or terminate early from the study, a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational

agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~4 weeks after an Early Termination visit).

g. 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 affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure) through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first.
h. Visual acuity must be assessed with the study eye chart. The patient should wear any prescription glasses or contacts during the assessment.
i. Papanicolaou test must be conducted for women without a test result within 6 months prior to the Screening 1 visit. The specimen should be submitted to the central laboratory during screening. Another test should be performed for inadequate or false-positive results and be submitted to the central laboratory.
j. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests.
k. At the Baseline Day 1 visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, levels of parathyroid hormone, thyroid-stimulating hormone, prolactin, Vitamin D, iron, ferritin, and hemoglobin A1c. An additional sample will be collected at this visit in all patients 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.
l. At the Week 24 visit or Early Termination visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
m. Pharmacokinetics samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics sample collections are complete.
n. Pharmacodynamic samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Early Termination and Follow Up visits when no dose is administered).
o. Pharmacogenomics sample: a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive).
p. Patients ≥ 39 years of age at the time of the anticipated Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period; if not, schedule at the Screening 1 visit.
q. Transvaginal ultrasound with or without transabdominal ultrasound must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm. Results must be submitted to and uterine fibroid criteria confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is required. See inclusion criterion #5 and exclusion criterion #1 for guidance as to when to perform a transabdominal ultrasound and saline or gel contrast. If saline or gel contrast is performed at Screening, it should also be performed at Week 24.
r. Obtain sample with a pipelle. Endometrial biopsy is performed at Screening 1 visit in all patients (and at Week 24 visit only if indicated [endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound]) and submitted to the central laboratory.

s. Procedure not required at the Early Termination Visit in patients whose last dose of study drug was during Week 6 or earlier. The procedure may be done if it will aid in the evaluation of an ongoing adverse event.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results will be available prior to randomization. Schedule the test at or shortly after the Screening 1 visit. Bone densitometry should be completed prior to the Screening 3 visit and as early as possible to ensure results are available prior to randomization.
u. Patient paper diary: Patients enter diary information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit. Patient eDiary: Ensure that eDiary data collection begins at least 7 days prior to Day 1. Patients enter eDiary information on a daily basis for their compliance with (study treatment starting at Baseline/Day 1), menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening 3 visit and compliance with study treatment starting at Baseline/Day 1 through Week 24 or Early Termination.
v. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

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

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

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies (including 1 in women with uterine fibroids and 1 in women with endometriosis) have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least 1 dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations of estradiol in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

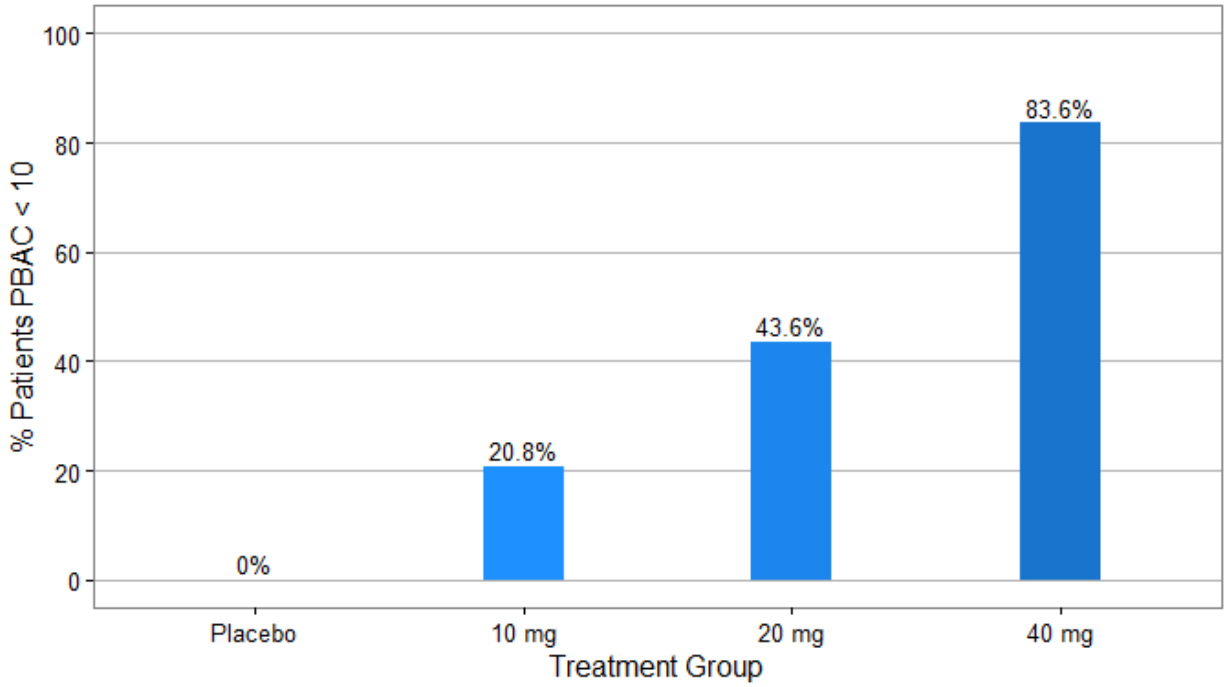
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 final analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤ 50 ng/dL) and maintained these levels through at least 24 weeks. These 24-week data were comparable to testosterone levels achieved by leuprolide 22.5 mg administered by injection every 3 months. Study C27003 also demonstrated rapid and sustained suppression of testosterone levels by relugolix for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. The serious identified risk associated with relugolix treatment is loss of bone mineral density in women. Nonserious adverse events related to relugolix class effects include hot flush and headache in both sexes; reproductive system events (abnormal uterine bleeding, genital hemorrhage, menorrhagia or heavy menstrual bleeding, menstruation irregular, and oligomenorrhea), arthralgia, and hyperhidrosis in women with uterine fibroids or endometriosis; and vision blurred, hepatic enzyme increased, libido decreased, and anxiety in men.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
<u>Primary Efficacy</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.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
<u>Secondary Efficacy</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.	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • 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

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.

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

≥ 160 mL for 1 cycle collected 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 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 the Screening visit.

A transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. A repeat endometrial biopsy will be performed at Week 24 only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). 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, paired endometrial biopsies in a subset of patients, 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 are provided in Figure 4-2.

Figure 4-1 MVT-601-3002 Study Schematic

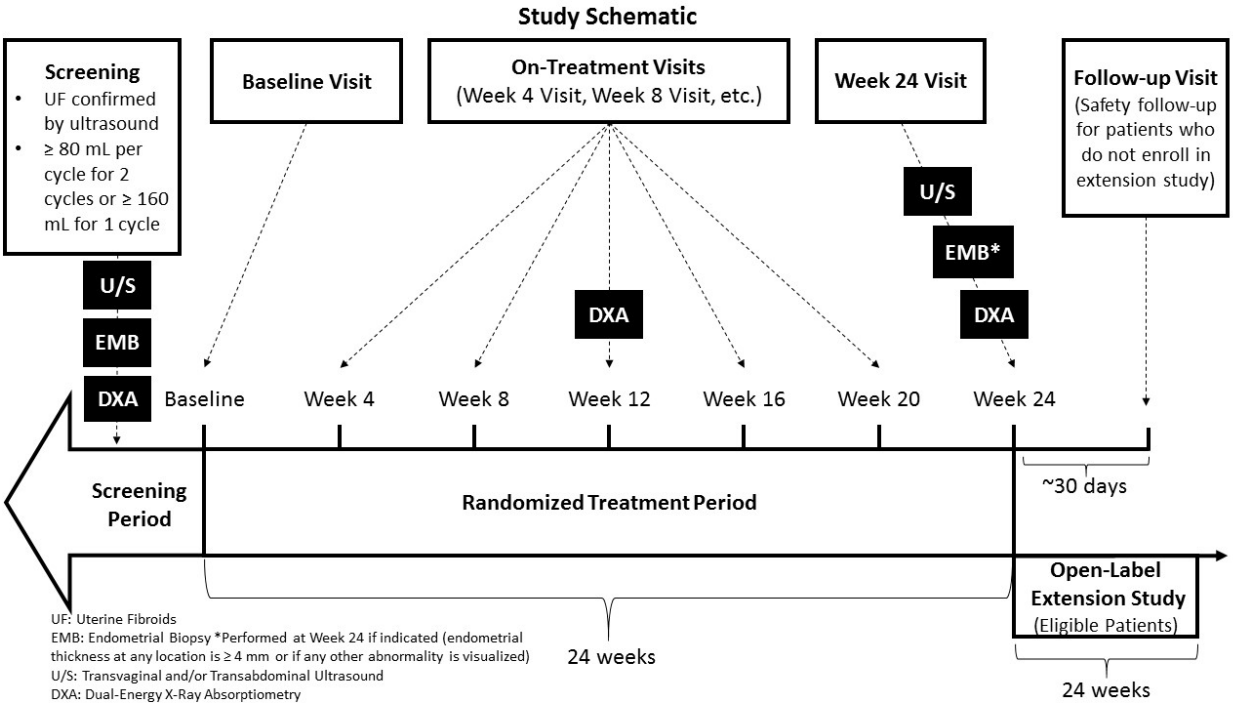


Figure 4-2 Schematic of MVT-601-3002 Screening Visit Scenarios

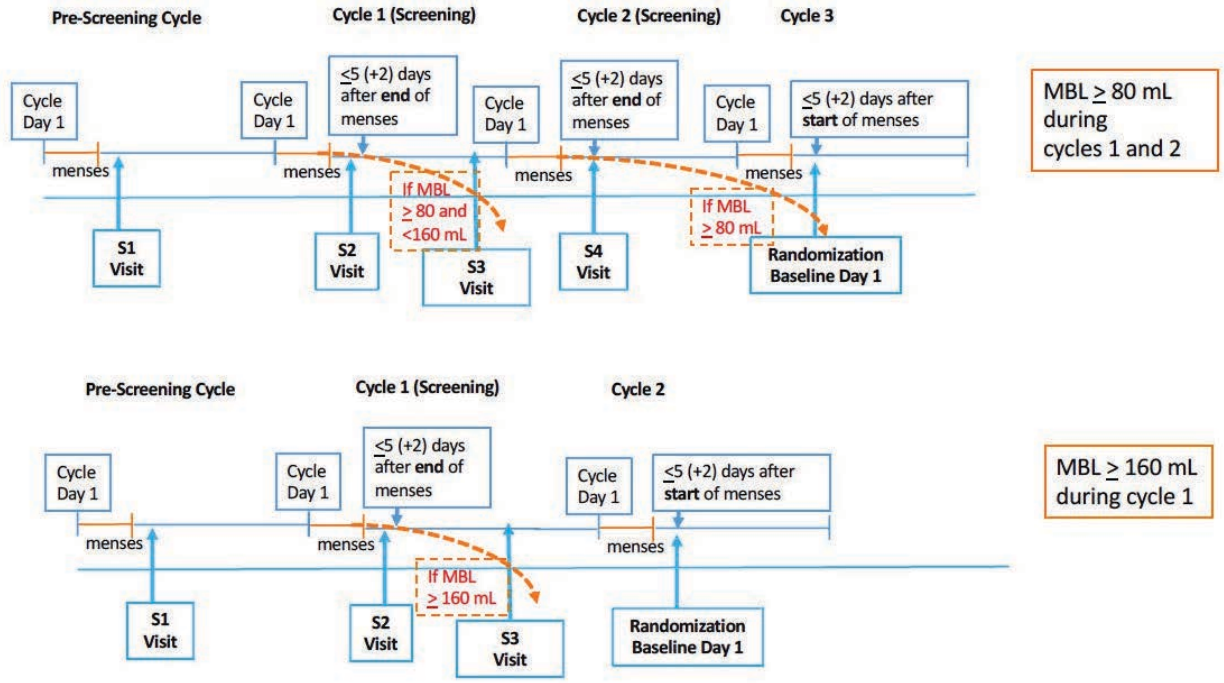


Figure 4-2

Screening visit 1 may be conducted at any time during the pre-screening cycle.

Top scenario:

- Eligibility is based on 2 consecutive screening cycles, each with ≥ 80 mL of menstrual blood loss assessed by the alkaline hematin method where the first screening cycle menstrual blood loss is also < 160 mL.

Bottom scenario:

- Eligibility is based on first screening cycle with ≥ 160 mL menstrual blood loss assessed by the alkaline hematin method.
- Patients whose first screening cycle MBL is < 80 mL and whose second screening cycle menstrual blood loss is ≥ 160 mL will follow the bottom scenario visit schedule.

Additional Scenarios (not depicted):

- Patients whose first screening cycle menstrual blood loss is < 80 mL and whose second screening menstrual blood loss is ≥ 80 mL but < 160 mL may collect menstrual blood loss during a third screening cycle if the first collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is ≥ 80 mL but < 160 mL and whose second screening menstrual blood loss is < 80 mL may collect menstrual blood loss during a third screening cycle if the second collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is < 80 mL may collect menstrual blood loss during a second cycle if the first collection was believed to be inadequate in a highly motivated patient. If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule.

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 for two cycles or ≥ 160 mL in one cycle during screening 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 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 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 28 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 associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for 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 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 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 Section 4.7) consistently, the screening period, and the randomized treatment period. However, the patient is not required to use dual contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion;
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: polyps ≤ 2.0 cm by ultrasound are not excluded;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the 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.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner;
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). A history of successfully treated hyperparathyroidism, hyperprolactinemia, or hyperthyroidism is allowed if the patient's bone mineral density is within normal limits;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;

10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with initial screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg on 2 repeat measures at least 15 minutes apart or diastolic blood pressure > 100 mmHg at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction or palpable thyroid abnormality (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
17. Is currently pregnant or lactating, or intends to become pregnant or to donate ova during the study period or within 2 months after the last dose of study drug;

18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study for other reasons, as determined by the investigator or sub-investigator or medical monitor.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

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

After a patient is screened, the investigator determines that the patient is eligible for enrollment, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's Baseline Day 1 visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IVRS/IWRS will also assign the Patient Identification Number.

4.6. Removal of Patients from Therapy

Completion of the Week 24 defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

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

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones are excluded, and patients must agree to use two forms of non-hormonal contraception (dual contraception), unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;

- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of dual contraception are:

- Condom with spermicide (cream, spray, foam, gel, suppository or polymer film);
- Diaphragm with spermicide (condom may or may not be used);
- Cervical cap with spermicide (condom may or may not be used); or
- Vaginal sponge impregnated with spermicide used with a condom.

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

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

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

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

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

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

Table 5-1 Description of MVT-601-3002 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An Swedish orange, over-encapsulated round film-coated white tablet with placebo back-fill material	A Swedish orange capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

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

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

5.2.1. Product Characteristics

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

Placebo to match relugolix is a pink tablet using common excipients.

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

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3002 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with relugolix placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

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

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

On clinic days, patients should be instructed not to eat or drink (other than water) prior to their clinic visit if the appointment is in the morning. If the appointment is later in the day, patients should not eat for at least 2 hours before the appointment and should also not to eat or drink (other than water) for at least 1 hour after administration of the study drug.

Patients should take any oral iron supplementation with meals.

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. Study drug can be held for a period of up to 2 weeks for evaluation and treatment of an adverse event. Patients may subsequently be re-started on study drug with the written approval of the sponsor (or designee).

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 35°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

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

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

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

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

Unblinding by the investigator for a given patient will occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Investigators will have direct access to a given patient's individual study treatment, however, the investigator should make every effort to first contact the medical monitor or appropriate study

personnel to discuss options **before** unblinding the patient's treatment assignment. If unblinding by the investigator occurs before sponsor personnel can be consulted or notified, the Investigator must notify the sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded patient. Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment.

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and prior to each visit, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused and used study drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment (ie, failure to take 80% or more of the scheduled doses after the last visit or compliance values over 120%), it may be appropriate to withdraw the patient from the study. All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zolendronic acid	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone	1 month

Drug Class	Examples	Window/Comments
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone	2 months (6 months for depot subcutaneous or intramusclar injections)
Estrogens	estradiol valerate conjugated estrogens	2 months (6 months for depot subcutaneous or intramusclar injections)
Oral Contraceptives	combined or progestin only	1 month for patients reporting a typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	1 week
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	No prior use if used for reduced bone mineral density
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin tranexamic acid vitamin k preparations factor Xa inhibitors	1 month

Drug Class	Examples	Window/Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	No window Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (≤ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	carbamazepine rifampin St John's wort	2 weeks Patients requiring a short course of these drugs during the study must contact the medical monitor for approval and guidance on study drug administration during this period.
Moderate and Strong P-glycoprotein Inhibitors	amiodarone azithromycin captopril carvedilol clarithromycin conivaptan cyclosporin diltiazem dronedarone erythromycin felodipine itraconazole ketoconazole lopinavir/ritonavir quercetin quinidine ranolazine ticagrelort verapamil	2 weeks (6 months for amiodarone) Patients requiring a short course of these drugs during the study must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone

5.10.2. Permitted Medications

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

5.10.2.1. Analgesics

From the Screening 1 visit to the Week 24 (or Early Termination) visit, the recommended analgesics for uterine-fibroid associated pain are as follows:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: investigator discretion

The purpose of these recommendations is to standardize, to the extent possible, analgesic medication use to facilitate the effects on the secondary endpoint regarding of uterine-fibroid-related pain.

Patients should be instructed not to use analgesics for prophylactic purposes.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL but ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.7. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities 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

- 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.

6.2.3. Screening 3 Visit

The patient will return for the Screening 3 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL and within ≤ 15 days after the Screening 2 visit. At the Screening 3 visit, 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. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. At this visit, review the endometrial biopsy results and review mammogram results, if available. Confirm that the bone densitometry scans have been submitted for central reading. The mammogram and central bone densitometry results must be available prior to randomization.

6.2.4. Screening 4 Visit

The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle. If not skipped, then the Screening 4 visit is scheduled to occur within 5 (+2) days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be 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.

6.2.5. Menstrual Blood Loss Repeat Collection

At the discretion of the investigator, the collection of menstrual blood loss can be repeated once during the screening period (either after the first or second screening cycle) 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.

6.2.6. Re-Screening

Patients who fail screening may be re-screened with approval of the medical monitor. Patients undergoing re-screening will sign a new informed consent form and issued a new screening number. For patients who begin re-screening within 10 weeks of signing the original informed consent form, transvaginal ultrasound, endometrial biopsy, and bone densitometry do not need to be repeated, if performed previously.

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, waist circumference, ECGs, clinical laboratory tests, pregnancy tests, and

adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12 and Week 24 visits. A repeat transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. An endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). The endometrial biopsy will be read centrally. 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/pharmacodynamic sampling. Patients must come to the clinic in the fasted state (eg, nothing to eat or drink other than water after midnight the day before the clinic visit) for the Baseline Day 1 and Week 24/Early Termination visits.

For visits other than Baseline Day 1 and Week 24/Early Termination, if the clinic visit cannot be scheduled for the morning, patients may eat in the morning but should not have eaten or had anything to drink other than water for at least 2 hours prior to the clinic visit and must not eat or drink (other than water) for at least 1 hour after the clinic visit. In these situations, the laboratory requisitions must indicate that the patient was not fasted for their chemistry and lipid testing.

6.4. Continuation into Extension Study

It is expected that most patients will enter the 28-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. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), endometrial biopsy, and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

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 prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, 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 investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Refer to the Schedule of Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, PK and pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

6.7. Study Procedures

6.7.1. Efficacy-Related Procedures

6.7.1.1. 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.

6.7.1.2. 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 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 pipelle should be used to obtain the specimen. A second biopsy is to be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). The biopsies will be read centrally.

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 will 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 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 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).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will be reviewed by the investigator to identify any potential adverse events.

Patients will also receive a paper diary to enter information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit.

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 and Health-Related 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.

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 sample of 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, 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.

6.7.2.2. 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 women without an available test result from within 6 months 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.

6.7.2.4. 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 Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Creatinine kinase Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine Microscopy
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones	**Serology**	**Iron Studies**
Thyroid-Stimulating Hormone Intact Parathyroid Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Vitamin D [25(OH)D]	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody	Iron Ferritin

A separate sample will be collected at the Day 1 visit in all patients and will be banked for hepatitis serology (Table 6-1) in all patients. The samples will be analyzed, if requested, by the medical monitor for evaluation of abnormal liver tests during the study.

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

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

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

6.7.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.7.2.6. Bone Mineral Density

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

The following will be assessed at each time point indicated for bone densitometry in the study Schedule of Activities (Section 1.1): 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, average bone mineral density of L1-L4, and T-score for average of L1-L4, total hip, and femoral neck.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual subject will be monitored by a central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the sties assessed during the study. In this case, repeat scan may be required for confirmation of the results, and it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for bone mineral density monitoring will be provided in the Study Reference Manual.

Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of blood collected for pharmacogenomics testing (see Section 6.7.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her

sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

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

7.1. Adverse Event Definitions

7.1.1. Adverse Event

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

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

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

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

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

7.1.2. Serious Adverse Event

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

a. Results in death;

b. Is life-threatening;

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

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from 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 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 affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Study procedure-related adverse events will be collected from the signing of the informed consent form.

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.

With the exception of adverse events that are considered related to study screening procedures, (which are to be recorded as adverse events), events 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. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

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

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

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

7.5. Adverse Events of Clinical Interest Reporting

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

Any ALT or AST elevation of this degree or greater occurring during the 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; or
- ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

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

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

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

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

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

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

7.6. Serious Adverse Event Reporting

Using a Safety 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:

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	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-601-3002)
- 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.

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

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

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for 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.

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, migraine with aura, porphyria, 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.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

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

8.2. Monitoring

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

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

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

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

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

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

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

9.2. Analysis Populations

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

The Per-Protocol Population will consist of those members of the ITT Population who have no major protocol violations. The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the ITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to breaking the study blind.

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

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 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.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the 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, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;

- 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, 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.

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 affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ class using MedDRA 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, 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), Z-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 incidence of vasomotor symptoms as assessed through adverse event reporting will be summarized by treatment arm.

The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar, total hip, or femoral neck) will be estimated with 95% confidence intervals by treatment group. Additional analyses will be performed to exam the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.5. Pharmacokinetic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

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

- Change from 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.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study participant. For studies conducted under a United States investigational

new drug application, the investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR 312), subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

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

10.1.4. Confidentiality

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

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

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

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

1) Investigator's study file. The investigator's study file will contain the IB, protocol/amendments, IRB or IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae, authorization and training forms, and other appropriate documents and correspondence.
2) Patient clinical source documents. The required source data should include the following for each patient:
   - Patient identification (name, date of birth, gender);
   - Documentation that the patient meets eligibility criteria, (eg, history, physical examination, and confirmation of diagnosis to support inclusion and exclusion criteria);
   - Participation in the study (including study number);
   - Study discussed and date of informed consent;
   - Dates of all visits;
   - Documentation that protocol-specific procedures were performed;
   - Results of efficacy parameters, as required by the protocol;

- Start and end date (including dose regimen) of study medication (drug dispensing and return should be documented as well);
- Record of all adverse events and other safety parameters (start and end date, and causality and intensity as assigned by the investigator);
- Concomitant medication (including start and end date); and
- Date of study completion and reason for early discontinuation, if applicable.

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

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

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

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

10.1.7. Electronic Case Report Forms

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

10.1.8. Investigational Product Accountability

The investigator or investigator's designee (ie, pharmacist) is responsible for ensuring adequate accountability (including dates and lot numbers) of all used and unused study drug (active and

placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient Identification Number, and the initials of the person dispensing the medication.

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

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

10.1.9. Inspections

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

10.1.10. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

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

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

10.2.2. Study Report

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

10.2.3. Posting of Information on Publically Available Clinical Trial Registers

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

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

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

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

10.3.2. Access to Information for Auditing or Inspections

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

10.3.3. Study Discontinuation

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

10.3.4. Publications

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

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

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

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

REFERENCES

ACOG Practice Bulletin No. 96: Alternatives to Hysterectomy in the Management of Leiomyomas. Obstetrics & Gynecology 2008;112(2 Part 1):387-400.

Activella FDA Clinical Pharmacology Review. November 1998. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20907.cfm. Accessed: 16 August 2016.

Activella US Prescribing Information. Revised 10/2013. Available at: http://www.novo-pi.com/activella.pdf. Accessed: 06 August 2016.

Archer DF, Chwalisz K, Feldman R, Stewart EA, Lukes AS, North J, Gao J, Williams LA, Jain R. Elagolix for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UF): Results from a phase 2A proof-of-concept study. American Society for Reproductive Medicine (Oct 17-21). October 20, 2015. Abstract O-181, available at: http://www.fertstert.org/article/S0015-0282(15)00717-7/pdf. Accessed: 08 July 2016.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. American Journal of Obstetrics and Gynecology 1992;166(2):740-5.

Cardozo ER. The estimated annual cost of uterine leiomyomata in the United States. American Journal of Obstetrics and Gynecology 2012;206(3):0092-0100.

Carr BR, Marshburn PB, Weatherall PT, Bradshaw KD, Breslau NA, Byrd W, Roark M, Steinkampf MP. An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial. Journal of Clinical Endocrinology & Metabolism 1993;76(5):1217-23.

Chwalisz K, Surrey E, Stanczyk FZ. The hormonal profile of norethindrone acetate: rationale for add-back therapy with gonadotropin-releasing hormone agonists in women with endometriosis. Reproductive Sciences 2012;19(6):563-71.

Food and Drug Administration (FDA). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. US Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. July2009.

Franke HR, van de Weijer PHM, Pennings TMM, van der Mooren MJ. Gonadotropin-releasing hormone agonist plus add-back' hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. Fertility and Sterility 2000;74(3):534-539. Available at: http://www.fertstert.org/article/S0015-0282(00)00690-7/pdf. Accessed: 16 August 2016.

Gliklich RE, Leavy MB, Velentgas P, Campion DM, Mohr P, Sabharwal R, Whicher D, Myers ER, Nicholson WK. Identification of Future Research Needs in the Comparative Management of Uterine Fibroid Disease. A Report on the Priority-Setting Process, Preliminary Data Analysis, and Research Plan. Effective Healthcare Research Report No. 31. (Prepared by the Outcome DEcIDE Center, under Contract No. HHSA 290-2005-0035-I, TO5). AHRQ Publication No. 11- EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available at: http://effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed: 16 August 2016.

Hallberg L, Nilsson L. Determination of menstrual blood loss. Scand J Clin Lab Invest. 1964;16(2):244–248.

Hapangama DK, Bulmer Judith N. Pathophysiology of heavy menstrual bleeding. Women's health 2016;12(1):3-13.

Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide Acetate Depot and Hormonal Add-Back in Endometriosis: A 12-Month Study. Obstetrics & Gynecology 1998;91(1):16-24.

Lee DY, Park HG, Yoon BKoo, Choi D. Effects of different add-back regimens on hypoestrogenic problems by postoperative gonadotropin-releasing hormone agonist treatment in endometriosis. Obstetrics & gynecology science 2016;59(1):32-8. Available at: http://synapse.koreamed.org/Synapse/Data/PDFData/3021OGS/ogs-59-32.pdf. Accessed: 16 August 2016.

Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2006;(2):CD003855.

Marret H, Fritel X, Ouldamer L, Bendifallah S, Brun J.L, De Jesus I, Derrien J, Giraudet G, Kahn V, Koskas M, Legendre G, Lucot J.P, Niro J, Panel P, Pelage J.P, Fernandez H. Therapeutic management of uterine fibroid tumors: updated French guidelines. European Journal of Obstetrics and Gynecology 2012;165(2):156-164.

Morris EP, Rymer J, Robinson J, Fogelman I. Efficacy of tibolone as add-back therapy' in conjunction with a gonadotropin-releasing hormone analogue in the treatment of uterine fibroids. Fertility and Sterility 2008;89(2):421-428.

Simpson PD, McLaren JS, Rymer J, Morris EP. Minimising menopausal side effects whilst treating endometriosis and fibroids. Post Reproductive Health: The Journal of the British Menopause Society. 2015;21(1):16-23.

Stewart EA. Clinical Practice. Uterine Fibroids. N Engl J Med. 2015;372(17):1646-55.

Wu D, Hu M, Hong L, Hong S, Ding W, Min J, Fang G, Guo W. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. Archives of Gynecology and Obstetrics 2014;290(3):513-523.

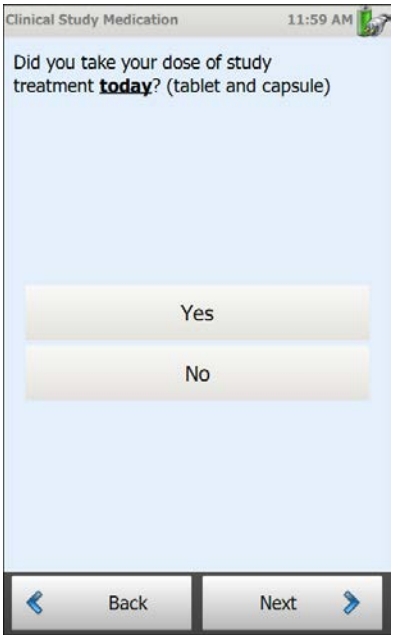
Zupi E, Marconi D, Sbracia M, Zullo F, De Vivo B, Exacustos C, Sorrenti G. Add-back therapy in the treatment of endometriosis-associated pain. Fertility and Sterility 2004;82(5):1303-1308.

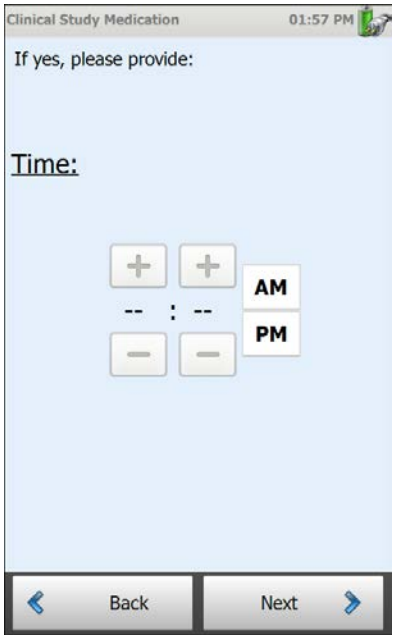
APPENDICES

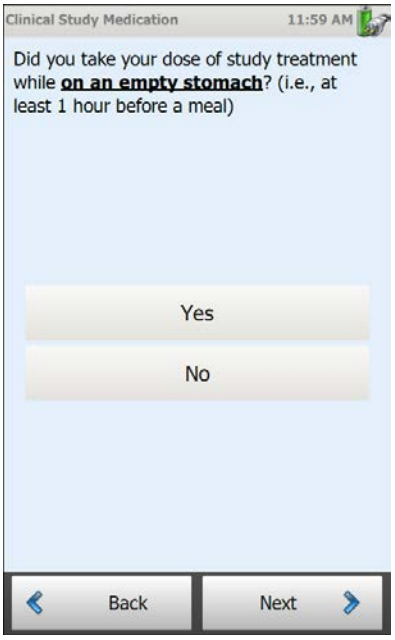
Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

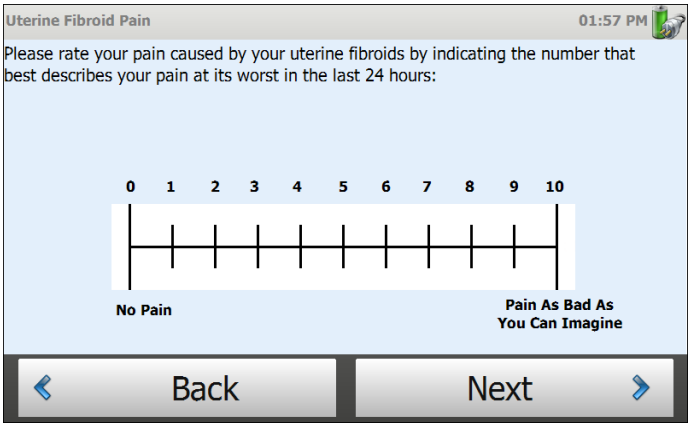
Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

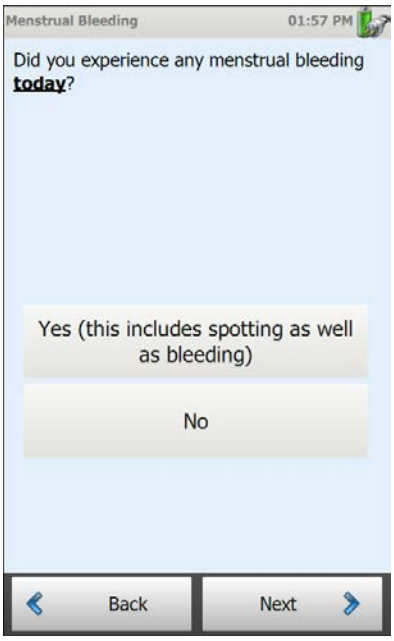
Appendix 2. Daily eDiary

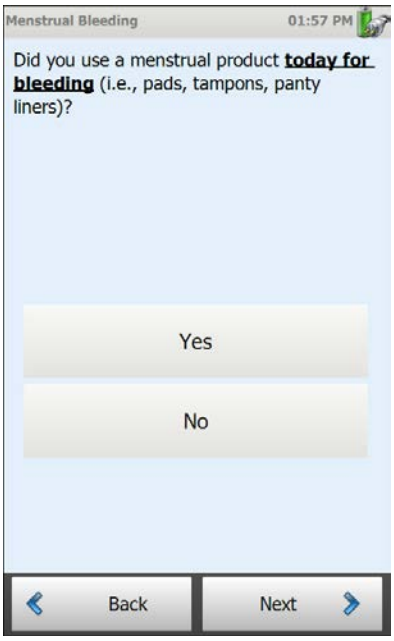


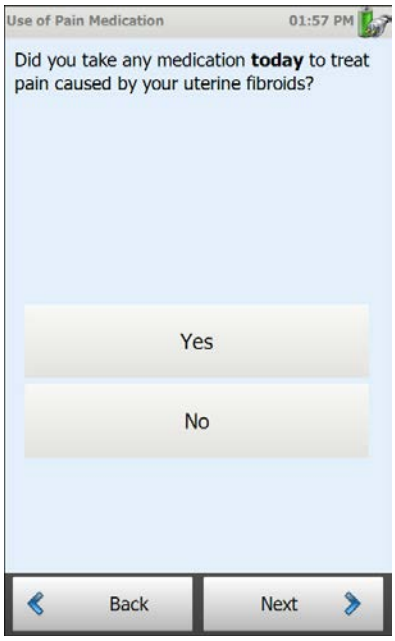


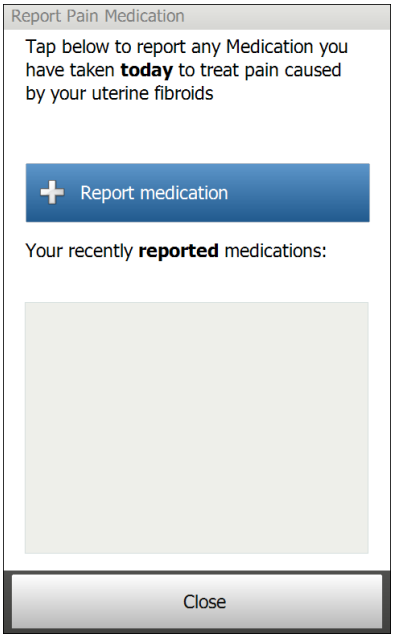


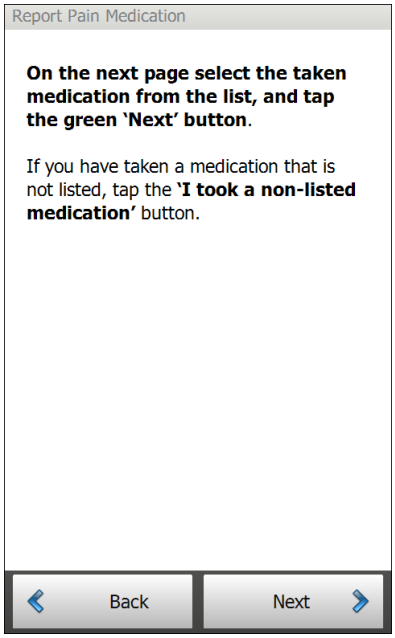



Menstrual Bleeding
01:57 PM
Did you experience any menstrual bleeding **today**?
Yes (this includes spotting as well as bleeding)
No
Back
Next

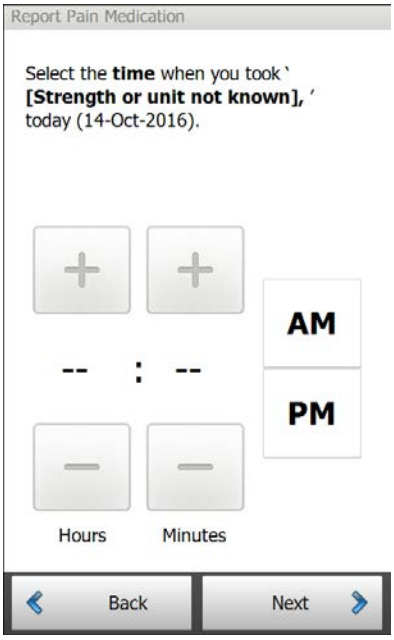

Menstrual Bleeding
01:57 PM
Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?
Yes
No
Back
Next


Use of Pain Medication
01:57 PM
Did you take any medication **today** to treat pain caused by your uterine fibroids?
Yes
No
Back
Next

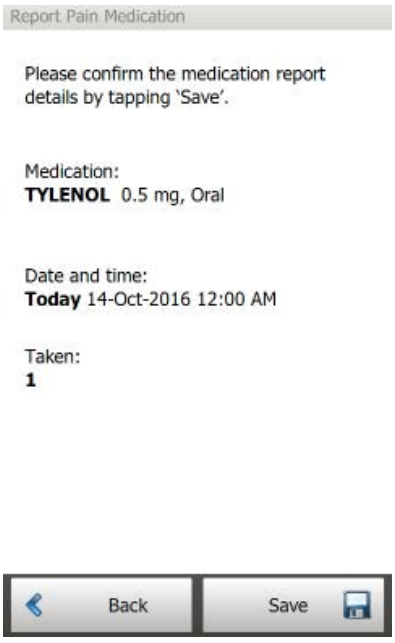

Report Pain Medication
Tap below to report any Medication you have taken **today** to treat pain caused by your uterine fibroids
Report medication
Your recently **reported** medications:
Close

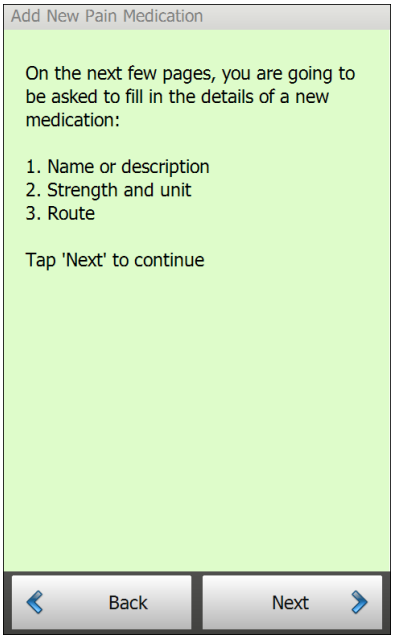

Report Pain Medication
On the next page select the taken medication from the list, and tap the green 'Next' button.
If you have taken a medication that is not listed, tap the **'I took a non-listed medication'** button.
Back
Next

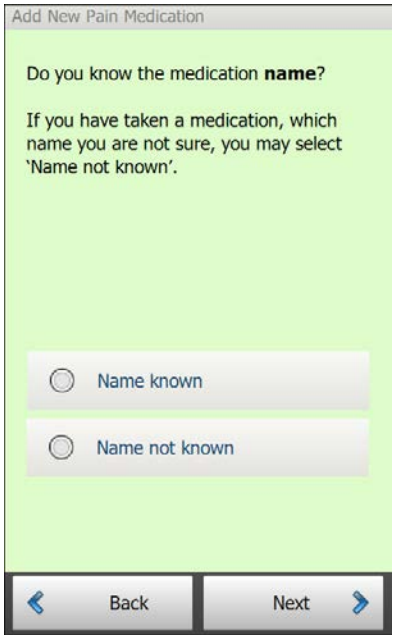

Report Pain Medication
Select the taken **medication** from the list and tap the green **'Next'** button.
I took a non-listed medication
Back
Next

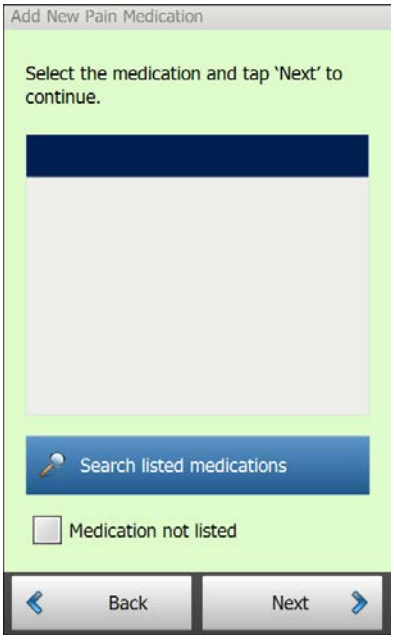

Report Pain Medication
Select the **time** when you took ' **[Strength or unit not known],** ' today (14-Oct-2016).
AM
PM
-- : --
Hours
Minutes
Back
Next

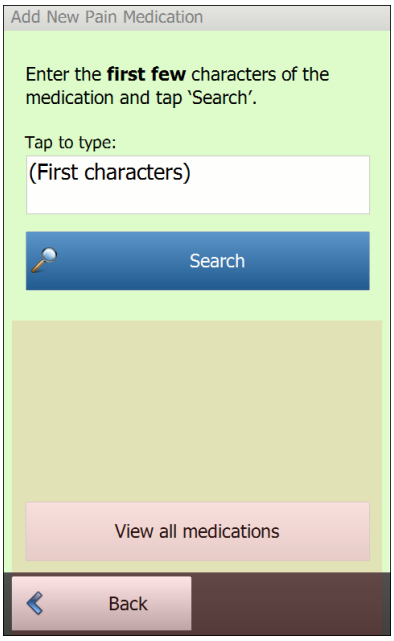

Report Pain Medication
Select the number of ' **[Strength or unit not known],** ' you took today (14-Oct-2016) at .
0 taken
Back
Next


Report Pain Medication
Please confirm the medication report details by tapping 'Save'.
Medication:
TYLENOL 0.5 mg, Oral
Date and time:
Today 14-Oct-2016 12:00 AM
Taken:
1
Back
Save

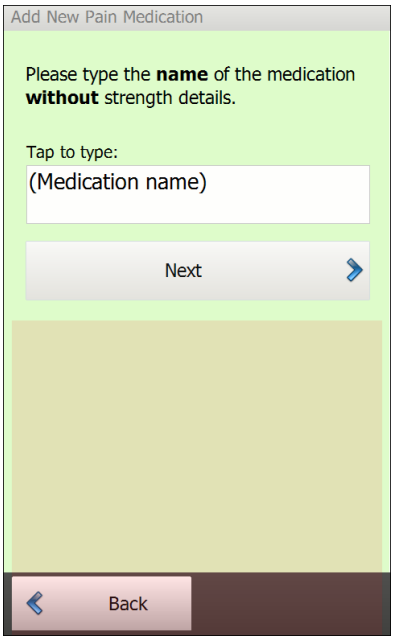

Add New Pain Medication
On the next few pages, you are going to be asked to fill in the details of a new medication:
1. Name or description
2. Strength and unit
3. Route
Tap 'Next' to continue
Back
Next

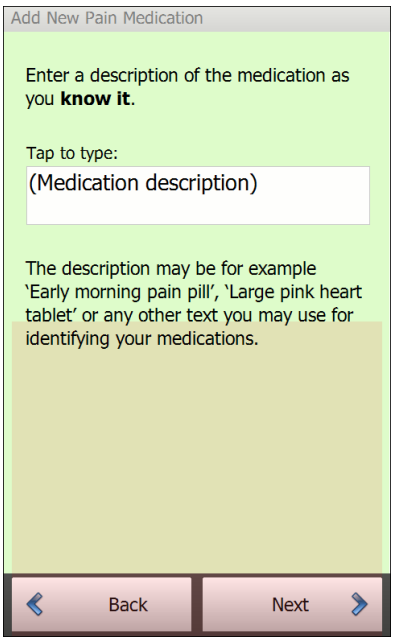

Add New Pain Medication
Do you know the medication **name**?
If you have taken a medication, which name you are not sure, you may select 'Name not known'.
Name known
Name not known
Back
Next

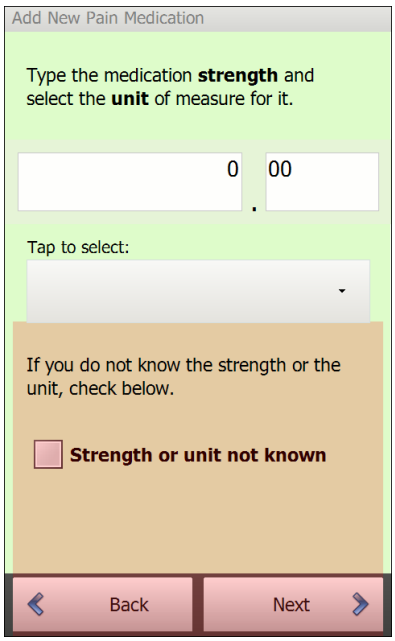

Add New Pain Medication
Select the medication and tap 'Next' to continue.
Search listed medications
Medication not listed
Back
Next

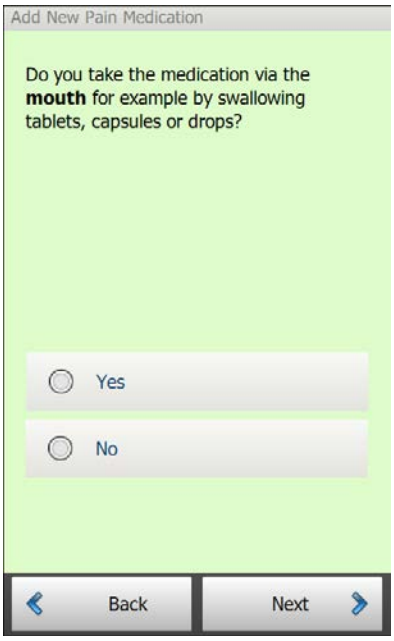

Add New Pain Medication
Enter the **first few** characters of the medication and tap 'Search'.
Tap to type:
(First characters)
Search
View all medications
Back


Add New Pain Medication
Select the medication and tap 'Next' to continue.
Medication not listed
Back
Next

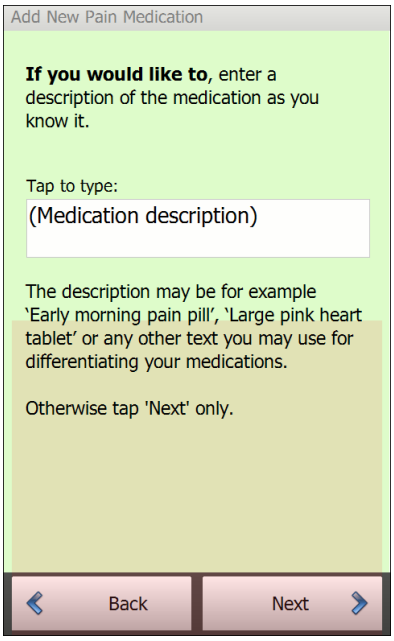

Add New Pain Medication
Please type the **name** of the medication **without** strength details.
Tap to type:
(Medication name)
Next
Back

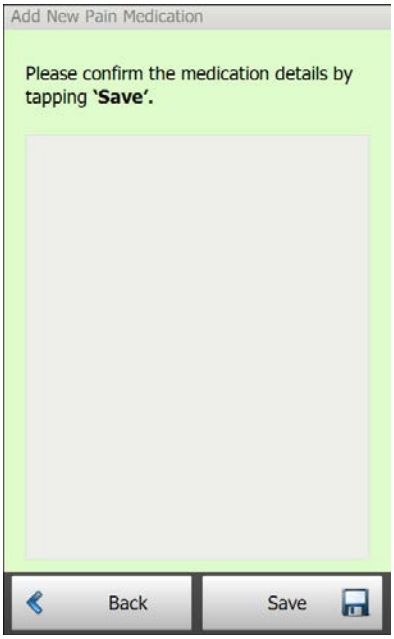

Add New Pain Medication
Enter a description of the medication as you **know it**.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for identifying your medications.
Back
Next

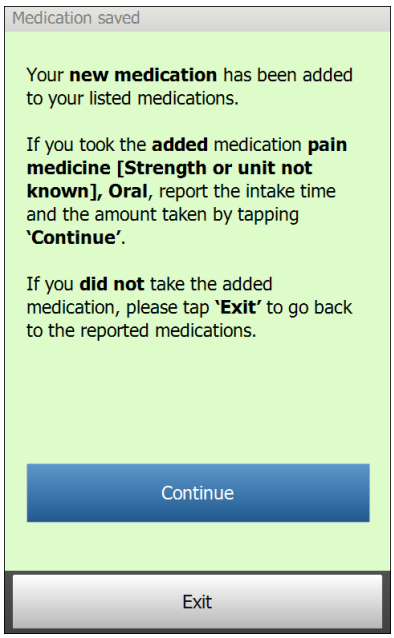

Add New Pain Medication
Type the medication **strength** and select the **unit** of measure for it.
0
00
Tap to select:
If you do not know the strength or the unit, check below.
Strength or unit not known
Back
Next


Add New Pain Medication
Do you take the medication via the **mouth** for example by swallowing tablets, capsules or drops?
Yes
No
Back
Next


Add New Pain Medication
Select the **route** for the medication:
Back
Next


Add New Pain Medication
If you would like to, enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for differentiating your medications.
Otherwise tap 'Next' only.
Back
Next


Add New Pain Medication
Please confirm the medication details by tapping **'Save'.**
Back
Save


Medication saved
Your **new medication** has been added to your listed medications.
If you took the **added** medication **pain medicine [Strength or unit not known], Oral**, report the intake time and the amount taken by tapping **'Continue'**.
If you **did not** take the added medication, please tap **'Exit'** to go back to the reported medications.
Continue
Exit

Appendix 3. Menorrhagia Impact Questionnaire

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

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

MIQ, Menorrhagia Impact Questionnaire.

Appendix 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

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

f:\institut\cultedep\project\hc1617\question\original\final\uterq.doc-21/12/2001

2

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

f:\institut\cultadap\project\hc1617\question\original\final\ufsorig.doc-21/12/2001

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 ❑

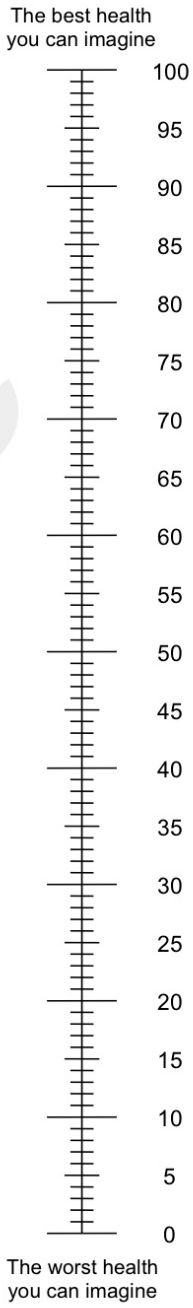
ANXIETY / DEPRESSION

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 ❑

2

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

YOUR HEALTH TODAY = ☐



Appendix 6. 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

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

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

- Detailed history of symptoms (eg, right upper quadrant pain, fatigue, nausea, vomiting, and fever);
- Prior and concurrent disease or illnesses;
- Exposure to environmental (eg, travel, new sexual exposure, exposure to ill family members or coworkers, etc) and/or industrial chemical agents;
- Prior and concurrent use of alcohol, recreational drugs, and special diets;
- Concomitant use of medications (including nonprescription medicines and herbal and dietary supplements), plants and mushrooms;
- Physical examination.

Recommended tests:

Also perform additional tests as clinically indicated or in consultation with a gastroenterologist or hepatologist.

- Repeat liver tests as per Appendix Table 1[a];
- Obtain gamma-glutamyl transferase, albumin, INR, and glucose in conjunction with repeat liver tests;
- CBC with differential to assess for eosinophilia;
- Serum acetaminophen (paracetamol) concentration;
- Obtain viral serologies for hepatitis A, B, C, D, and E; consider testing for Epstein Barr virus;
- Evaluate for alcoholic hepatitis, nonalcoholic steatohepatitis, biliary tract disease, autoimmune hepatitis, etc.;
- Serology for celiac disease;
- Appropriate liver imaging;
- Hepatology consult (liver biopsy may be considered in consultation with a hepatologist or gastroenterologist).

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

CLINICAL STUDY PROTOCOL

Study Title:	LIBERTY 2: 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
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3002
Indication:	Treatment of heavy menstrual bleeding associated with uterine fibroids
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifier(s):	EudraCT # 2016-005113-50 IND # 131161
Version and Effective Date:	Original: 10-NOV-2016 Amendment 1: 10-FEB-2017 Amendment 2: 25-SEP-2017

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

LIBERTY 2: 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-601-3002

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

PPD

_____	25-Sep-2017 Date
_____	25-Sep-2017 Date
_____	25-Sept-2017 Date
_____	25-Sep-2017 Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from time 0 to 24 hours
BMI	body mass index
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
di-22:6-BMP	di-22:6-bis(monoacylglycerol)phosphate
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
FDA	(United States) Food and Drug Administration
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
ITT	Intent-to-Treat (Population)
IVRS/IWRS	Interactive Voice/Web Recognition Service
LFT	liver function tests
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
MIQ	Menorrhagia Impact Questionnaire
mmHg	millimeters of mercury
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PBAC	Pictorial Blood Loss Assessment Chart
PD	Pharmacodynamics
PGA	Patient Global Assessment

Term	Explanation
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

1. PROTOCOL SYNOPSIS

Study Title	LIBERTY 2: 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-601-3002
Location	Multinational, including North and South America, South Africa, and Europe
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 uterine fibroids on symptoms, activities, and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for function and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire (MIQ); o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.

	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 percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • 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; • To determine the incidence of vasomotor symptoms with 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. 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 (EQ-5D-5L).

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 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 ≥ 160 mL during 1 cycle during the screening period. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during 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. Another transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). 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 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, paired endometrial biopsies in a subset of patients, 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.

During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the day immediately before to the Week 24 visit.

Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where 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 patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).

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 contraception during the study and for 30 days following the last dose of study drug. Specifically agrees to use non-hormonal contraception, as described in Section 4.7 consistently during the Screening period and the Randomized Treatment Period and either nonhormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient is not required to use specified non-hormonal contraception if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
   c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described in Section 4.7;
   d. Practices total abstinence from sexual intercourse as her preferred lifestyle; periodic abstinence is not acceptable;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or < 2 cm are eligible;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study.

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the 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.);

2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;
10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline

Day 1 visit);

b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, or Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening or Baseline Day 1 ECG electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
    d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitic

syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted; 17. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug; 18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary window periods for these medications are also described therein); 19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation; 20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders V (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form); 21. Has participated in a previous clinical study that included the use of relugolix; 22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling); 23. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor; 24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.	
Dose and Route of Administration	Test Product (Group A and Group B) • Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated. • Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated. Reference Product (Group C) • Group C: Placebo relugolix manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color.

Duration of Treatment	Study treatment will be administered for 24 weeks (randomized treatment period). For women who do not to enroll in an open-label extension study, there is a 30-day follow-up period after the end of treatment (ie, after the patient's last dose of study medication).
Criteria for Evaluation	Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment: • Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate; • Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate. Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the two relugolix groups for both efficacy and safety. <u>Primary Efficacy Endpoint</u> • Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

	Secondary Efficacy Endpoints • Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment; • 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 impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to 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.

	Safety Endpoints • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), total hip, and femoral neck as assessed by DXA; • Incidence of vasomotor symptoms. Pharmacokinetic and Pharmacodynamic Endpoints • Pre-dose trough concentrations (Cτ) 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 Endpoint • 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.

Statistical Methods

Efficacy

The efficacy analyses will be conducted using an Intent-to-Treat (ITT) Population defined as all randomized patients, unless otherwise specified in the statistical analysis plan. Randomization will be 1:1:1 with the stratification variables of geographic region and mean screening menstrual blood loss volume (mL per alkaline hematin method) as follows:

- Geographic Region: North America versus Rest of World;
- Mean screening menstrual blood loss volume: < 225 mL versus ≥ 225 mL.

The randomization stratification factors will be incorporated into inferential testing of all efficacy endpoints, unless otherwise specified.

The primary hypothesis tested in this study is whether relugolix co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate is superior to placebo in the percentage of women 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 on treatment as compared with Baseline.

The point estimate and 2-sided 95% confidence interval of the difference in the proportion will be calculated between the relugolix Group A and placebo Group C. The between-treatment comparisons will be performed using the Cochran-Mantel-Haenszel method.

The comparisons of the relugolix arms versus placebo will be performed for the secondary efficacy and safety endpoints using appropriate statistical methods. Comparisons between the two relugolix arms will be descriptive. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and secondary endpoint testing. Details of this procedure will be provided in the statistical analysis plan.

Sample Size

Assuming a placebo control response rate of 25%, the assessment of the superiority of relugolix 40 mg co-administered with low-dose hormonal add-back therapy (Group A) versus placebo (Group C) in the 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, a sample size of 260 (130

patients in each of the relugolix and placebo arms) will provide > 99% power to detect a difference of greater than 30 percentage points using a 2-sided test at significance level of 0.05. The total sample size for the study will be approximately 390 patients (130 patients in each of the 3 arms).

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms, paired endometrial biopsies in a subset of patients, and assessments of bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of study drug (safety population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute's CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the Baseline, Week 12, and Week 24 visits and the absolute, percent, and standardized changes from baseline will be summarized. Vasomotor adverse events will be separately summarized.

A chartered independent Data and Safety Monitoring Board will monitor all available safety data, including bone density assessments, on an ongoing basis during this study.

Pharmacokinetics and Pharmacodynamics

The PK concentration data (relugolix, estradiol, and norethindrone pre-dose) and pharmacodynamics concentration data (LH, FSH, estradiol, and progesterone pre-dose) will be listed and summarized by treatment arm and visit. In addition, the PK data from this study will be combined with PK data from other studies to define a population PK model, which will be reported separately. Exposure-response analyses of the primary efficacy endpoint and safety will be conducted to assess the effect of relugolix exposure on outcomes.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3002

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Day of Study Drug Treatment					**1**	**29**	**57**	**85**	**113**	**141**	**169**		**197**
Visit Window Timing (days)		Within 5 (+2) days after completion of Screening 1 menses	Within ≤ 15 days after Screening 2 visit	Within 5 (+2) days after completion of 2nd Screening menses	Within 7 days of the start of menses	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**	**-10/+20**		**-3 to + 10**
Informed Consent	X												
Medical History	X												
Review Eligibility Criteria	X		X	X	X								
Vital Signs	X		X		X	X	X	X	X	X	X	X[e]	X
Waist Circumference					X								
Height	X												
Weight	X				X						X	X[e]	X
Temperature	X				X						X	X[e]	X
Adverse Event Collection[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Visual Acuity[h]					X						X	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Complete Physical excluding GYN Examination	X				X						X		
GYN Examination with Pap Test, if applicable	X[i]												
Signs and Symptoms-Directed Physical Exam			X			X	X	X	X	X		X[e]	X
12-Lead Electrocardiogram			X		X			X			X	X[e]	X
Clinical Laboratory Tests[j]	X	X			X[k]	X	X	X	X	X	X[l]	X[e]	X
PK Sample[m]					X	X		X			X	X[e]	
PD Sample[n]					X	X		X			X	X[e]	X
Daily Study Drug Administration					X (Day 1 through day *immediately prior* to Week 24/Early Termination visit)							X[e]	
Administer Dose of Study Drug in Clinic					X	X	X	X	X	X		X[e]	
PGx Sample[o]					X							X[e]	
Pregnancy Test (Urine)	X		X		X	X	X	X	X	X	X	X[e]	X
Urinalysis	X				X						X	X[e]	
Mammogram[p]	schedule	X											
Transvaginal Ultrasound (with or without Transabdominal Ultrasound)[q]	X										X[s]	X[e]	
Endometrial Biopsy[r]	X										X[s, w]	X[e]	
Bone Densitometry[t]	schedule	X						X			X[s, x]	X[e]	

	SCREENING PERIOD[a]				RANDOMIZED TREATMENT PERIOD								SAFETY FOLLOW-UP
VISIT NAME	**Screening 1**	**Screening 2[b]**	**Screening 3[c]** (if MBL is ≥ 80 mL at 1st Screening menses)	**Screening 4[b]** (Skip if MBL ≥ 160 mL at 1st Screening menses)	**Baseline Day 1[d]** (if MBL is ≥ 80 mL in 2 cycles or ≥ 160 mL in 1 cycle	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24 (or Early Termination of Study Drug)**	**Unscheduled**	**Follow-up[f]** (~30 days after last dose of study drug)
Randomization					X								
Dispense Feminine Products	X	X			X	X	X	X	X	X		X[e]	
Dispense Study Treatment					X	X	X	X	X	X		X[e]	
Patient paper diary/ eDiary[u]	X	X	X	X	X	X	X	X	X	X	X	X[e]	
Feminine Product Collection and Venous Blood Sample[v]		X		X		X	X	X	X	X	X	X[e]	
MIQ					X	X	X	X	X	X	X	X[e]	
UFS-QOL					X			X			X	X[e]	
EQ-5D-5L					X						X	X[e]	
PGA for function[y]					X	X	X	X	X	X	X	X[e]	
PGA for symptoms[y]					X	X	X	X	X	X	X	X[e]	
Treatment Compliance and Study Drug Accountability[z]						X	X	X	X	X	X	X[e]	
Status of Menstruation Recovery													X

Notes:
Abbreviations: DXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; GYN, gynecology; MBL, menstrual blood loss; MIQ, Menorrhagia Impact Questionnaire; Pap, Papanicolaou; PD, pharmacodynamics; PGA, Patient Global Assessment; PGx, pharmacogenomics; PK, pharmacokinetics; UFS-QOL, Uterine Fibroid Symptom and Health-Related Quality of Life.
For patients who are re-screening, please see Section 6.2.6 for abbreviated screening procedures.

a. The screening period should be initiated after the informed consent form is signed and any exclusionary windows for prohibited medications has been confirmed.
b. Visit to occur within 5 (+2) days of the completion of menses. Visit 4 should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle.

c. Visit to occur within ≤ 15 days after Screening 2 visit; eDiary dispensation must occur at least 7 days prior to Baseline Day 1. The alkaline hematin menstrual blood loss collection may be repeated once at the discretion of the investigator if one menstrual cycle does not meet menstrual blood loss criteria thought to be due to inadequate collection for a highly motivated patient.
d. The Baseline Day 1 visit should occur within 7 days of the onset of menses. The following procedures must be completed prior to randomization: urine pregnancy, vital signs, waist circumference, weight, temperature, complete physical examination, visual acuity assessment,12-lead ECG, and review of eligibility criteria. Collect clinical laboratory sample, PK sample, pharmacodynamic sample, and urinalysis prior to first dose of study drug. Whenever possible, complete MIQ, UFS-QOL, PGA for symptoms and PGA for function, and EQ-5D-5L prior to the first dose of study drug.
e. For an Unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit. The last dose of study drug in the Randomized Treatment Period will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit is defined as the last day on which a Week 24 visit procedure is conducted.
f. Follow-up visit: For women who do not continue into the open-label extension study (MVT-601-3003) and/or terminate early from the study, a follow-up visit to assess safety will be scheduled approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first (ie, ~Week 28 for patients who complete the study or ~30 days after an Early Termination visit).
g. 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 affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Collect nonserious adverse event information from the Baseline Day 1 visit (or from the time of signed informed consent if event was related to a screening study procedure) through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first.
h. Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100; continue as far as the patient can go per the testing instructions. See Study Reference Manual for additional instructions on visual acuity testing and see Section 6.8.2.8 for overall guidance including follow-up.
i. Papanicolaou test must be conducted for women without a test result within 2 years prior to the Screening 1 visit. The specimen should be submitted to the central laboratory during screening. Another test should be performed for inadequate or false-positive results and be submitted to the central laboratory.
j. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count. Samples should be obtained in the fasted state (no food or drink other than water after midnight) for the Baseline and Week 24 visit clinical laboratory tests. In addition to clinical chemistries and a complete blood count, include thyroid-stimulating hormone at Screening 1. Screening laboratory tests may be repeated during the screening period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor. 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 reported through the central lab.
k. At the Baseline Day 1 visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, prolactin, Vitamin D, and hemoglobin A1c. An additional sample will be collected at this visit in all patients 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.
l. At the Week 24 visit or Early Termination visit, obtain clinical laboratory tests after an overnight fast (other than water) of at least 8 hours. In addition to clinical chemistries and a complete blood count, include a lipid profile, thyroid-stimulating hormone, prolactin, and hemoglobin A1c.
m. Pharmacokinetics samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for PK analysis of relugolix, estradiol (PK lab), and norethindrone. Instruct the patient not to take her study treatment at home on these visit days and to record the time of her previous dose (ie, the dose taken the day before the visit). Administer study drug after PK and pharmacodynamics

sample collections are complete (Study drug is not administered at Week 24 Visit; for patients proceeding into the extension study, refer to protocol for study MVT-601-3003).

n. Pharmacodynamic samples: Samples should be obtained in the fasted state since study drug is administered on an empty stomach (see Section 5.4). Collect pre-dose samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations. Administer study drug after PK and pharmacodynamic sample collections are complete (with the exception of Early Termination and Follow Up visits). Study drug is not administered at the Week 24 Visit for patients proceeding into the extension study (refer to protocol for study MVT-601-3003).
o. Pharmacogenomics sample (unless precluded by local law or regulations): a separate pharmacogenomics consent is required before this sample may be collected. If possible, the pharmacogenomic sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive)
p. Patients ≥ 39 years of age at the time of the anticipated Baseline Day 1 visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period; if not, schedule at the Screening 1 visit.
q. Transvaginal ultrasound with or without transabdominal ultrasound must be performed to confirm the presence of uterine fibroids and the absence of any other pathology that might be responsible for the increase in menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm. Results must be submitted to and uterine fibroid criteria confirmed by a central reader prior to randomization into the study. Note: Transvaginal ultrasound is required. See inclusion criterion #5 and exclusion criterion #1 for guidance as to when to perform a transabdominal ultrasound and saline or gel contrast. If transabdominal ultrasound or ultrasound with saline or gel contrast is performed at Screening, it should also be performed at Week 24.
r. Obtain sample with an endometrial suction curette (eg, Pipelle®). Endometrial biopsy is performed at Screening 1 visit in all patients (and Week 24 Visit only if indicated [endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound]) and submitted to the central laboratory. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis.
s. Procedure not required at the Early Termination Visit in patients whose last dose of study drug was during Week 6 or earlier. The procedure may be done if it will aid in the evaluation of an ongoing adverse event.
t. Bone densitometry (L1-L4, total hip, femoral neck) will be assessed during the screening period and the central results will be available prior to randomization. Schedule the test at or shortly after the Screening 1 visit. Bone densitometry should be completed prior to the Screening 3 visit and as early as possible to ensure results are available prior to randomization.
u. Patient paper diary: Patients enter diary information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit. Patient eDiary: Ensure that eDiary data collection begins at least 7 days prior to Day 1. Patients enter eDiary information on a daily basis for their compliance with study treatment starting at Baseline/Day 1, menstrual bleeding and use of feminine products for menstrual bleeding, uterine fibroid-associated pain by the Numerical Rating Scale, and use of pain medications (analgesics) starting at Screening 3 visit through Week 24 or Early Termination.
v. Hemoglobin: a venous blood sample must be collected each time feminine products are collected to be sent to the central laboratory conducting the alkaline hematin assessment.
w. Patients not proceeding to the extension study who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will be followed and will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination visit (see Section 6.7). The repeat biopsy will be submitted to the central laboratory.
x. Schedule DXA as early as possible within the Week 24/Early Termination visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo another DXA scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted about medications and conditions

(eg, pregnancy) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.

y. Patient will enter responses in a paper questionnaire at the site.
z. The patient should be asked to bring all study drug to the clinic at each visit. Please refer to Section 5.8.

2. INTRODUCTION

2.1. Uterine Fibroids with Heavy Menstrual Bleeding

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

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

Combined hormonal contraceptives and progestational agents are commonly prescribed to regulate abnormal uterine bleeding, but appear to have limited efficacy in the treatment of uterine fibroids [Carr, 1993]. Although no randomized studies evaluating the use of levonorgestrel-releasing intrauterine system devices for the treatment of heavy menstrual bleeding related to uterine fibroids have been conducted, observational studies have reported a reduction in uterine volume and bleeding and this system is approved for use by the United States (US) Food and Drug Administration (FDA).

Gonadotropin-releasing hormone (GnRH) agonists such as leuprolide acetate (also known as leuprorelin) are effective in lowering estrogen and progesterone levels, decreasing menstrual bleeding, and decreasing fibroid size, however they cannot be used for more than 6 months due to bone mineral density loss from the resulting hypoestrogenic state. The GnRH agonists, which

are administered by injection at 1- or 3-month intervals, first stimulate secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) which, in turn, increase estradiol and progesterone levels resulting in a flare of clinical symptoms. This initial rise in hormonal levels is followed by a gradual decline in levels over 4 weeks as the pituitary becomes desensitized to the chronic stimulation of the GnRH agonist and LH and FSH levels fall. Other medical treatments are used but have limited clinical effectiveness, including tranexamic acid, aromatase inhibitors, non-steroidal anti-inflammatory medications, and danazol.

The current mainstay of treatment for women with heavy menstrual bleeding associated with uterine fibroids is surgery. Several surgical procedures are frequently performed including myomectomy by various techniques, endometrial ablation, endometrial uterine artery embolization, and magnetic resonance-guided focused-ultrasound surgery. Each of these procedures has complications. For example, abdominal myomectomy results in complications requiring hysterectomy in up to 3 to 4% of cases, along with the frequent development of intraoperative adhesions [Gliklich, 2011]. Furthermore, recurrence after myomectomy is common with at least 25% of women requiring additional treatment [Stewart, 2015, Marret, 2012, ACOG Practice Bulletin No. 96, 2008]. Hysterectomy is the definitive procedure and more than 250,000 hysterectomies are performed in the US for uterine fibroids. Major complications have been reported to occur in up to 25% of women undergoing hysterectomy, including infection, severe bleeding, and injuries to the urethra, bowel or bladder. One study showed that among women with Medicaid insurance who underwent abdominal hysterectomy, there was a 10% risk of transfusion and up to a 28% risk of medical or surgical complications including major blood loss, wound infection and febrile episodes [Gliklich, 2011].

Approximately 3 million women in the United States suffer from symptomatic uterine fibroids that are inadequately treated with medical therapy, and related US health care costs for uterine fibroids exceeds $34 billion [Stewart, 2015; Cardozo, 2012, Gliklich, 2011]. There is a great need for a medicine that can decrease the symptoms of uterine fibroids and can be safely administered so that women have an option other than surgical procedures such as myomectomy and hysterectomy.

2.2. Relugolix

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of heavy menstrual bleeding associated with uterine fibroids. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1 mg and 0.5 mg once daily, respectively.

2.2.2. Pharmacology

Relugolix (also known as TAK-385) is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure. Relugolix was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

2.2.3. Nonclinical Toxicology

A comprehensive package of nonclinical studies has been conducted to evaluate the toxicity of relugolix. These include repeat-dose toxicity studies in mice of up to 13 weeks, in rats of up to 26 weeks, and in monkeys of up to 39 weeks. Oral administration of relugolix resulted in reversible liver toxicity (liver enzyme elevations with and without accompanying histopathological correlates) and changes related to reversible phospholipidosis (PLD) in several tissues/organs, most notably the lymph nodes, lungs, and testes in rats; and lymph nodes, parietal cells in the stomach, spleen, and intestines in monkeys. PLD by itself is not adverse, and no significant adverse effects were associated with PLD in rats and monkeys except at doses that caused mortality in rats (≥ 1000 mg/kg/day), which were associated with extremely high systemic exposures. The no-observed-effect level (NOEL) for liver findings in the 39-week monkey toxicity study was 5 mg/kg/day, and the no-observed-adverse-effect level (NOAEL) is considered to be 15 mg/kg/day. The gender combined mean end of study area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) at the NOAEL of 15 mg/kg/day was 5.2 μg·hr/mL, which is ~51 times higher than the estimated exposure (AUC) in women receiving 40 mg once daily (0.101 μg·hr/mL), the dose of relugolix to be administered in this study. Both the liver and PLD findings demonstrated evidence of reversibility following a 13-week recovery period in monkeys. No evidence of PLD has been observed in clinical studies. The relugolix toxicology program supports the conduct of clinical studies up to the NOAEL (15 mg/kg/day) exposure (5.2 μg·hr/mL) for liver toxicity in monkeys (most sensitive species).

Relugolix is not mutagenic or clastogenic and was not carcinogenic in 2-year mouse and rat studies. Embryo-fetal death was observed only in relugolix-treated pregnant rabbits, but no fetal malformation was observed in rat and rabbit embryo-fetal development studies. While relugolix demonstrated phototoxic potential in an in vitro 3T3 neutral red uptake assay, in vivo data did not show phototoxicity in hairless mice, and no damage to the eye structure or function was evident in the 4- and 39-week monkey toxicity studies. Prolongation of the corrected QT interval was observed in a study of cynomolgus monkeys at ≥ 100 mg/kg (estimated C_{max} of 4.0 μg/mL), but did not prolong the QT interval in a human thorough QT study at doses up to 360 mg (C_{max} of 0.181 μg/mL).

2.2.4. Previous Human Experience

Nine phase 1 studies in healthy volunteers and 3 phase 2 studies (including 1 in women with uterine fibroids and 1 in women with endometriosis) have been completed. In addition, 6 clinical studies evaluating relugolix are ongoing, including 2 phase 1 studies, 2 phase 2 studies in men with prostate cancer (US and Europe), and 2 phase 3 studies in women with uterine fibroids in Japan. More than 1380 patients and healthy volunteers have received at least 1 dose of relugolix, including 158 women receiving relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men receiving relugolix at doses of 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks. Eighty-eight women have been treated with relugolix 40 mg once daily for 24 weeks.

2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

Data from phase 1 studies demonstrate that relugolix treatment results in rapid, dose-dependent suppression of estradiol in female subjects and testosterone in male subjects. After oral administration, the absolute bioavailability of relugolix was 12% (range 6 to 25%) with a predominant elimination half-life of 37 to 42 hours. In a human radiolabeled study, there were no major circulating metabolites of relugolix. The primary route of elimination of drug-related material was in the feces. The pharmacokinetics (PK) and pharmacodynamics of relugolix have been evaluated, and appear to be similar in American and Japanese volunteers, despite the lower mean body mass index observed in Japanese volunteers.

A phase 1 study (TAK-385_101) in healthy US premenopausal women demonstrated the tolerability of single doses of relugolix 1 to 80 mg, and once-daily dosing of relugolix at 10, 20, and 40 mg for 2 weeks. Plasma concentrations of relugolix increased in a slightly greater than dose-proportional manner. Suppression of serum estradiol was similar after single doses of 40 or 80 mg once daily relugolix. The serum concentrations of LH, FSH, estradiol, and progesterone rapidly decreased and remained at low levels with multiple doses of relugolix with the majority of women having estradiol levels < 10 pg/mL in the 40-mg dose group. Based on these hormone reductions, oral relugolix 40 mg once daily was chosen as the high dose for further study in phase 2.

A 6-week phase 1 study (MVT-601-1001) in healthy US premenopausal women was conducted to evaluate the safety, PK, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1 mg/0.5 mg once daily). Median pre-dose trough concentrations of estradiol in the relugolix alone arm were ~6 pg/mL; with the addition of 1 mg estradiol once daily, these were increased to ~26 pg/mL, and median peak concentrations were ~45 pg/mL. This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992]. Relugolix PK and norethindrone acetate PK were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all PK samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

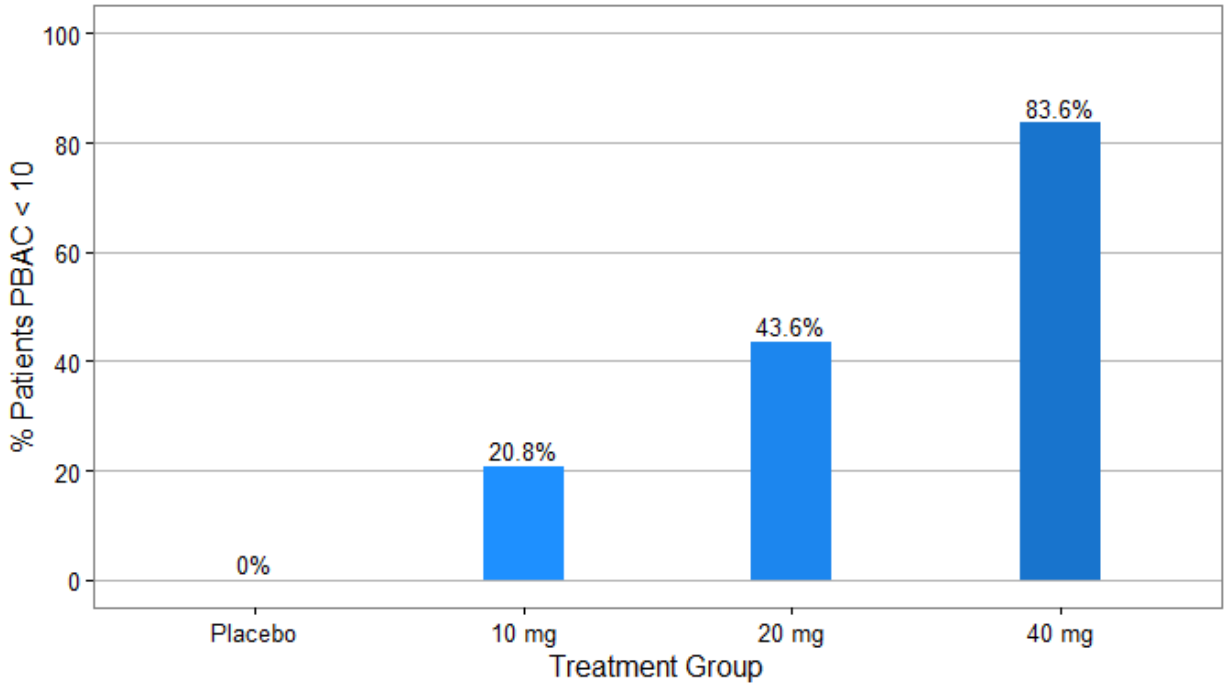
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors

of P-glycoprotein (P-gp) up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the corrected (QTc) interval.

2.2.4.2. Clinical Studies in Women with Uterine Fibroids or Endometriosis and Men with Prostate Cancer

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, PK, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo (Figure 2-1). The proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

Figure 2-1 Percent of Women with Markedly Decreased Blood Loss at End of Treatment Period after Once Daily Administration of Relugolix (Study CCT-001)



Notes: Data shown is Pictorial Blood Loss Assessment Chart (PBAC) method of assessing blood loss during Week 6 to Week 12. Primary endpoint is proportion of patients with PBAC score < 10.
Statistically significant difference with $p < 0.001$ observed for each relugolix treatment arm versus placebo.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient and tinnitus, libido decreased, menopausal depression and hyperhidrosis in one patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation [SD]) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± SD) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks). Estradiol levels were suppressed for the duration of the study.

In the 12-week phase 2 endometriosis study (CCT-101) and the companion 12-week extension study (OCT-101; total of 24 weeks of treatment), the safety profile of the relugolix 40 mg once daily dose was comparable to that of leuprolide treatment. The most commonly reported treatment-emergent adverse events in the relugolix groups than in the placebo group included hot flush, metrorrhagia, and menstruation irregular, and were considered to be due to the pharmacological effects of relugolix. The events of menstrual bleeding were primarily reported in the first 28 days. Bone mineral density changes from baseline (mean ± standard deviation [SD]) observed after 24 weeks of treatment were -0.23 ± 1.986% in the placebo group, -1.61 ± 2.338%, -2.58 ± 2.936%, and -4.90 ± 2.912% in the relugolix 10, 20, and 40 mg groups respectively, and -4.43 ± 2.157% in the leuprolide group. Bone mineral density changes from baseline in the relugolix 40 mg group at 12 and 24 weeks were comparable to those in the leuprolide group for the same durations. Two patients had liver test abnormalities considered study drug-related by the investigator and that resulted in discontinuation of study drug.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Data from these ongoing studies are not available.

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Study C27002, which remains ongoing, enrolled patients with advanced prostate cancer. In this open-label, parallel group study, men were randomized to receive oral relugolix at a dose of 80 mg or 120 mg once daily after a single oral loading dose of 320 mg (N = 50 in each arm) or to the GnRH agonist therapy, leuprolide acetate, 22.5 mg administered subcutaneously every 12 weeks, (N = 25) for up to 48 weeks. Study C27003, in which the last clinical study visits have been completed, enrolled men in North America or the United Kingdom requiring six months of androgen deprivation therapy as neoadjuvant and adjuvant therapy to external beam radiation therapy. Patients were randomized to relugolix 120 mg once daily (after a single oral loading dose of 320 mg) (N = 65) or to degarelix 80 mg subcutaneously every four weeks (N = 38) for 24 weeks (after a single loading dose of 240 mg). Results from the C27002 final analysis demonstrated that both doses of oral relugolix, 80 mg and 120 mg once daily, rapidly reduced testosterone levels below the castration threshold (≤ 50 ng/dL) and maintained these levels through at least 24 weeks. These 24-week data were comparable to testosterone levels achieved by leuprolide 22.5 mg administered by injection every 3 months. Study C27003 also demonstrated rapid and sustained suppression of testosterone levels by relugolix for the 24-week treatment duration.

In an interim analysis of the phase 2 prostate cancer study C27002, the most common treatment-emergent adverse events occurring in at least 10% of men with advanced prostate cancer in the relugolix 80 mg or 120 mg once daily arms or leuprolide arm included hot flush, alanine aminotransferase increase, fatigue, aspartate aminotransferase, diabetes mellitus, hyperhidrosis, muscle spasm, injection site reaction, and frequent daytime urination. The common adverse events observed with relugolix in men with prostate cancer were generally consistent with its mechanism of action and those observed with leuprolide. A biomarker for PLD, di-22:6-bis(monoacylglycerol)phosphate (di-22:6-BMP), was monitored in this study due to findings of PLD in nonclinical toxicity studies. There were no systematic increases in post-baseline serum or urinary di-22:6-BMP levels and no changes exceeding 2-fold observed in any patients.

No clinical evidence of relugolix-related PLD-associated toxicity has been observed regarding the heart, liver, central nervous system, or muscle in any clinical study.

Relugolix has been generally well tolerated. Adverse drug reactions associated with relugolix in women with uterine fibroids or endometriosis include hot flush, headache, hyperhidrosis and bone density decreased. Adverse drug reactions associated with relugolix in men with prostate cancer include hot flush, fatigue, arthralgia, nausea, weight increased, gynecomastia and night sweats.

More detailed description of the results of phase 1 and phase 2 studies in women with uterine fibroids and endometriosis and in men with prostate cancer are provided in the relugolix Investigator Brochure, along with a full discussion of the safety profile of relugolix.

3. STUDY OBJECTIVES AND ENDPOINTS

Inferential efficacy assessments will be made between the following groups and placebo Group C after 24 weeks of study treatment:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;
- Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.

Descriptive assessment of treatment effect will be made between each relugolix group (Group A and Group B) and placebo (Group C) for safety outcomes and between each of the two relugolix groups for both efficacy and safety.

Objective(s)	Endpoint(s)
<u>Primary Efficacy</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.	• Proportion of women in the relugolix Group A versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35days of treatment, as measured by the alkaline hematin method.
<u>Secondary Efficacy</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 uterine fibroids on symptoms, activities and health-related quality of life as measured by components of the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL); o Patient global assessment for function and symptoms as measured by the Patient Global Assessment (PGA) for function	• Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method. The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively: • Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method; • Change from Baseline to Week 24 in menstrual blood loss; • Proportion of women who achieve amenorrhea over the last 35 days of treatment; • Proportion of women with a hemoglobin

Objective(s)	Endpoint(s)
and symptoms; o Impact of heavy menstrual bleeding on social, leisure, and physical activities as measured by the Menorrhagia Impact Questionnaire; o Pain associated with uterine fibroids; o Uterine volume; and o Uterine fibroid volume.	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 impact of uterine fibroids based on the UFS-QOL activities domain; • Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11; • Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20; • Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29; • Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity; • Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life; • Change in PGA for uterine fibroid related function from Baseline to Week 24; • Change in PGA for uterine fibroid symptoms from Baseline to 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	• Treatment-emergent adverse events, change

Objective(s)	Endpoint(s)
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 percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B in women with heavy menstrual bleeding associated with uterine fibroids; • 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; • To determine the incidence of vasomotor symptoms with 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.	in vital signs (including weight), clinical laboratory tests, and electrocardiograms; • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by DXA; • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (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 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.
<u>Exploratory</u>	
• 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 (EQ-5D-5L).	• 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 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 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 ≥ 160 mL during 1 cycle during the screening period. Women with iron-deficient microcytic anemia and hemoglobin ≥ 8 g/dL and ≤ 10 g/dL during 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. Another transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at Week 24. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). 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 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, paired endometrial biopsies in a subset of patients, 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.

During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug for the Randomized Treatment Period will be taken on the immediate day prior to the Week 24 visit.

Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where 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 patient's last dose of study drug. Patients who are not proceeding to the extension study and who have endometrial hyperplasia or endometrial cancer on the endometrial biopsy or bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to the baseline measurement will undergo further testing and follow-up to evaluate recovery (see Section 6.6). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.6). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8.2.8).

A schematic of the overall study design is provided as Figure 4-1. Details of the screening period visits are provided in Figure 4-2.

Figure 4-1 MVT-601-3002 Study Schematic

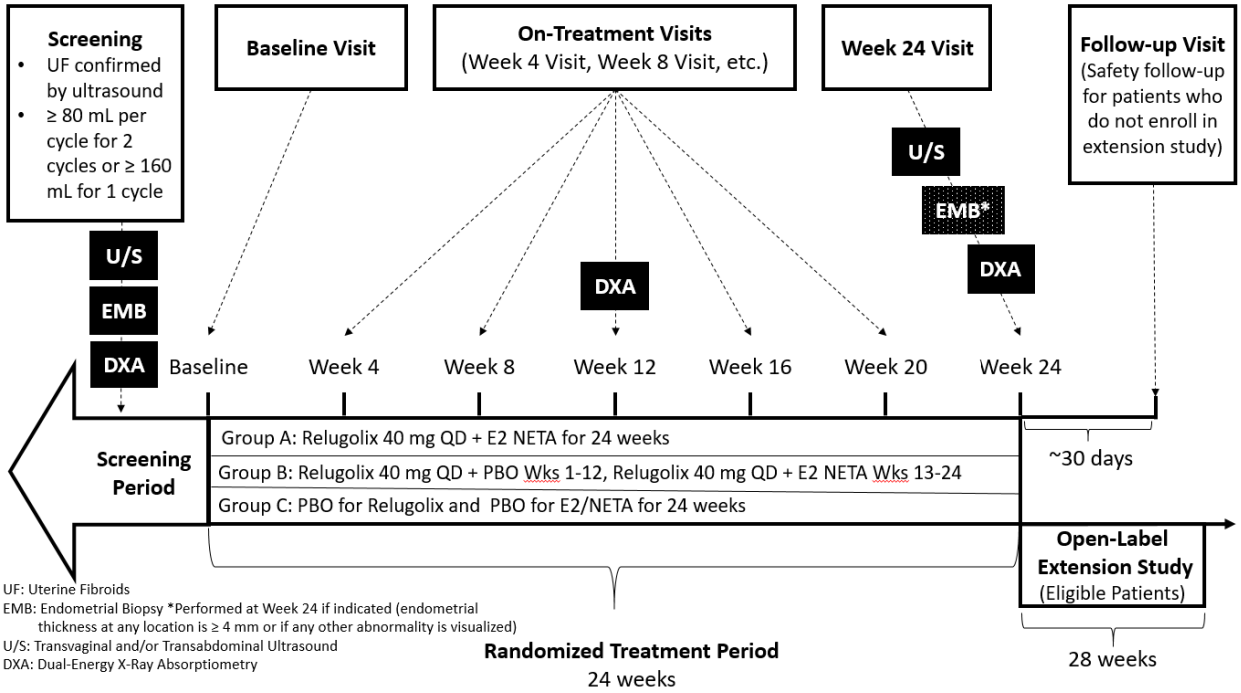


Figure 4-2 Schematic of MVT-601-3002 Screening Visit Scenarios

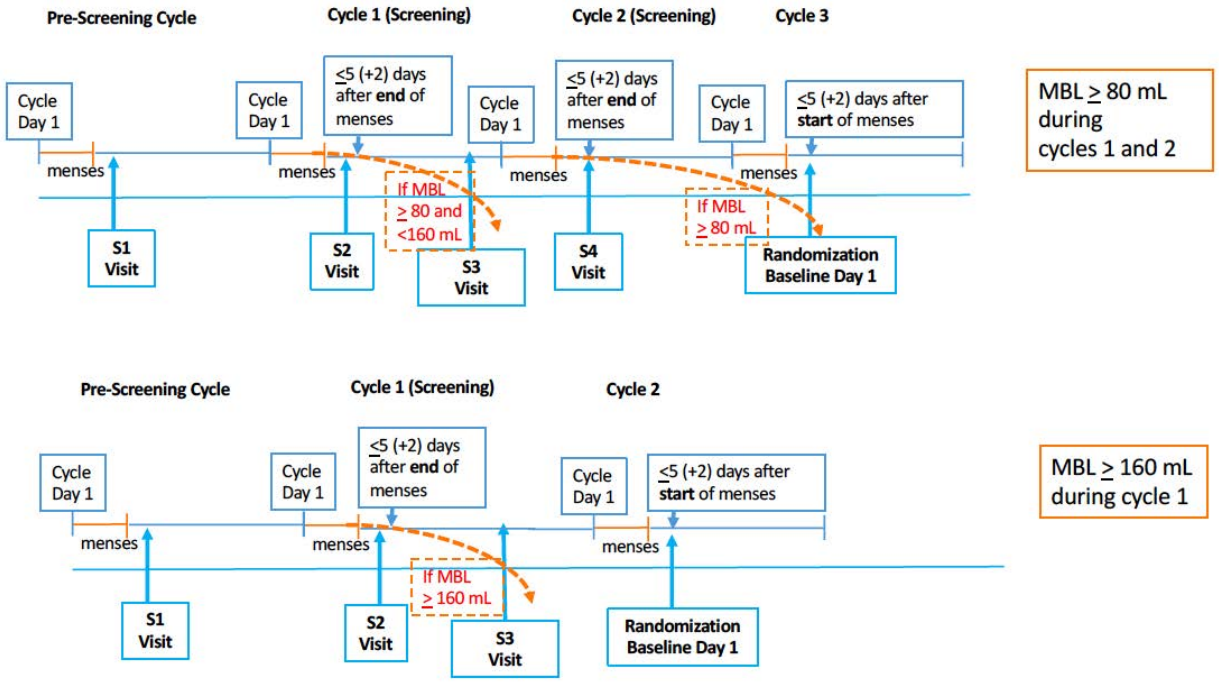


Figure 4-2

Screening visit 1 may be conducted at any time during the pre-screening cycle.

Top scenario:

- Eligibility is based on 2 consecutive screening cycles, each with ≥ 80 mL of menstrual blood loss assessed by the alkaline hematin method where the first screening cycle menstrual blood loss is also < 160 mL.

Bottom scenario:

- Eligibility is based on first screening cycle with ≥ 160 mL menstrual blood loss assessed by the alkaline hematin method.

Additional Scenarios (not depicted):

- Patients whose first screening cycle menstrual blood loss is < 80 mL and whose second screening menstrual blood loss is ≥ 80 mL but < 160 mL may collect menstrual blood loss during a third screening cycle if the first collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is ≥ 80 mL but < 160 mL and whose second screening menstrual blood loss is < 80 mL may collect menstrual blood loss during a third screening cycle if the second collection was believed to be inadequate in a highly motivated patient.
- Patients whose first screening cycle menstrual blood loss is < 80 mL may collect menstrual blood loss during a second cycle if the first collection was believed to be inadequate in a highly motivated patient. If the second screening menstrual blood loss is ≥ 160 mL, the patient should follow the top scenario visit schedule, and the patient does not need to collect menstrual blood loss for another cycle.

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 for two cycles or ≥ 160 mL in one cycle during screening 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 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 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 28 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 associated with uterine fibroids (≥ 80 mL per cycle for 2 cycles or ≥ 160 mL for 1 cycle as measured by the alkaline hematin method during the screening period).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or patient safety. Therefore, adherence to the criteria as specified in the protocol is essential. Any questions regarding patient eligibility and entry criteria should be discussed with the medical monitor.

4.3.1. Inclusion Criteria

A woman will be eligible for 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 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 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 contraception during the study and for 30 days following the last dose of study drug. Specifically agrees to use non-hormonal contraception, as described in Section 4.7 consistently during the Screening period and the Randomized Treatment Period and either nonhormonal or oral contraceptives after return of menses following treatment discontinuation. However, the patient is not required to use specified non-hormonal contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the screening period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 4 months prior to the first screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described in Section 4.7;
9. Has an adequate endometrial (aspiration) biopsy performed during the screening period, with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer). Note: Patients for whom polyps are detected on biopsy but are either not evident on ultrasound or < 2 cm are eligible;
10. If ≥ 39 years of age at the time of the Baseline Day 1 visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent) during the screening period or within 6 months prior to the screening period.

4.3.2. Exclusion Criteria

1. Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding, such as uterine or cervical polyps ≥ 2.0 cm, large simple ovarian cyst > 4.0 cm, endometrioma(s) > 4.0 cm, or any other clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

   Note: Saline or gel contrast is not routinely required. Use of such contrast is required only when the 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.);
2. Has known rapidly enlarging uterine fibroids in the opinion of the investigator;
3. Has undergone myomectomy, ultrasound-guided laparoscopic radiofrequency ablation, or any other surgical procedure for fibroids, uterine artery embolization, magnetic resonance-guided focused ultrasound for fibroids, as well as endometrial ablation for abnormal uterine bleeding within 6 months prior to the Screening 1 visit;
4. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement or spinal hardware in the lumbar spine);
5. Has a baseline bone mineral density z-score < -2.0 at spine, total hip, or femoral neck;
6. Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). Patients whose hyperparathyroidism or hyperthyroidism has been successfully treated or whose hyperprolactinemia has been successfully treated and/or who meet bone mineral density eligibility criteria for the study are allowed;
7. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
8. Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction;
9. Gastrointestinal disorder affecting absorption or gastrointestinal motility;

10. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
11. Has jaundice or known current active liver disease from any cause, including hepatitis A (HAV IgM), hepatitis B (HBsAg), or hepatitis C (HCV Ab positive, confirmed by HCV RNA);
12. Has any of the following cervical pathology: high grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high risk human papilloma virus testing is negative or if DNA testing for human papilloma virus 16 and 18 is negative;
13. Has any of the following clinical laboratory abnormalities at any screening visit:
    a. Hemoglobin < 8.0 g/dL (patients with screening hemoglobin results < 8 g/dL may be prescribed iron supplements and have their hemoglobin levels retested prior to the Baseline Day 1 visit);
    b. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 x ULN on clinical laboratory testing at either the Screening 1 or Screening 2 visit (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
    c. Estimated glomerular filtration rate < 60 mL/min/m^2 using the Modification of Diet in Renal Disease method;
    d. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
    e. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

14. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart at any screening visit or the Baseline Day 1 visit;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening electrocardiogram unless judged by the investigator to be due to physical fitness;
15. Has been a participant in an investigational drug or device study within the 1 month prior to Screening 1 visit;
16. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than curatively treated nonmelanoma skin cancer or surgically cured Stage 0 in situ melanoma;
    c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to Screening or is expected to change during the study should not be enrolled;
    d. Has a systemic autoimmune disease (eg, systemic lupus erythematosus, Sjogren syndrome, rheumatoid arthritis, polymyositis, systemic sclerosis, psoriasis,

psoriatic arthritis, vasculitic syndromes, etc). Psoriasis not requiring or anticipated to require systemic therapy is permitted;

17. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug;
18. Is currently using any prohibited medications as detailed in Section 5.10.1 (suitable exclusionary periods for these medications are also described therein);
19. Has a contraindication or history of sensitivity to any of the study treatments or components thereof; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
20. Has a prior (within 1 year of Screening 1 visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use and this should be documented in the electronic case report form);
21. Has participated in a previous clinical study that included the use of relugolix;
22. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
23. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor;
24. Has received a blood transfusion within 8 weeks prior to Screening Visit 1 or during the screening period.

4.4. Screening

Screening numbers will be assigned to each patient who signs an informed consent form and begins the screening period. Screening failures are patients who consent to participate in the clinical study but are never randomized.

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

After a patient is screened, the investigator determines that the patient is eligible for enrollment, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the Interactive Web Response System (IWRS) during the patient's Baseline Day 1 visit. The IWRS will assign the patient a study treatment kit number available at the site according to the randomization code. The IWRS will also assign the Patient Identification Number (Randomization Number).

4.6. Removal of Patients from Therapy

Completion of the Week 24 defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (Week 24 visit) on the Schedule of Activities and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- Corrected QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who have a clinically significant decrease in visual acuity as evaluated by an ophthalmologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol's requirements. This may include < 75% compliance with the study drug for at least 2 months; not returning any feminine products despite having menstrual bleeding for > 2 consecutive cycles; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days of eDiary completion;
- Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain

contact with the patient. The site should attempt at least three documented telephone calls and if necessary a certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study, including through 30 days following the last dose of study drug, unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure), at least 4 months prior to the first Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

The only acceptable methods of contraception for those for whom one of the above methods do not apply are:

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

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

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

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

5. TREATMENTS

5.1. Treatments Administered

In this study, patients will be randomized to receive one of the following blinded oral study treatments:

- 24 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 12 weeks of relugolix 40 mg tablet plus a placebo capsule followed by 12 weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate; OR
- 24 weeks of relugolix placebo tablet plus a placebo capsule.

Each patient will be instructed to take one tablet and one capsule per day. The last dose of study drug will be taken on the day immediately before the Week 24 visit. Note: Week 24 visit data is defined as the last day on which a Week 24 visit procedure is conducted.

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

Table 5-1 Description of MVT-601-3002 Study Drugs

Name of Investigational Product	Relugolix	Relugolix Placebo	Estradiol / Norethindrone Acetate	Estradiol / Norethindrone Acetate Placebo
Formulation Description	Round film-coated pink tablet	Round film-coated pink tablet	An Swedish orange, over-encapsulated round film-coated white tablet with placebo back-fill material	A Swedish orange capsule with placebo back-fill material
Dosage Form	Tablet	Tablet	Capsule	Capsule
Unit Dose Strength	40 mg	0 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg	0 mg
Route of Administration / Duration	Oral once daily/ 24 weeks	Oral once daily/ 24 weeks	Oral once daily/ 12 or 24 weeks	Oral once daily/ 12 or 24 weeks

5.2. Identity of Investigational Product

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

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

5.2.1. Product Characteristics

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

Placebo to match relugolix is a pink tablet using common excipients.

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

Placebo to match the over-encapsulated estradiol/norethindrone acetate combination product is a capsule containing back-fill material only.

5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to one of the following treatment arms:

Table 5-2 Protocol MVT-601-3002 Treatment Group Randomization

Treatment Group	Randomized Treatment	Approximate Number of Patients
Group A	Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks	130
Group B	Relugolix 40 mg tablet co-administered with estradiol / 0.5 mg norethindrone acetate placebo tablet for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks	130
Group C	Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks	130

Randomization will be stratified by geographic region and mean screening menstrual blood loss as follows:

- Geographic region: North America versus Rest of World; and
- Mean screening menstrual blood loss measured by the alkaline hematin method: < 225 mL versus ≥ 225 mL.

Patients are assigned to one of the three treatment arms in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

5.4. Directions for Administration

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

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

On selected clinic days, study drug will be administered in the clinic (refer to Sections 1.1 and Section 6.3) or the visits during which patients take study drug in the clinic rather than at home)

Patients will hold their study treatment on clinic visit days and record the time of their previous dose (ie, the time that they took their dose on the day before the clinic visit); they will be instructed to take their study treatment in the clinic after PK and pharmacodynamic samples are collected.

5.5. Dose Reduction/Dose Administration

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

5.6. Storage, Packaging, and Labeling

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

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

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

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

5.7. Blinding

All patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data and Safety Monitoring Board if requested. The blind will be maintained during assessment of PK and pharmacodynamic testing; PK concentrations will be reported to the sponsor in a blinded fashion, or only after database lock and unblinding, or provisions will be made to provide data only to personnel approved for unblinding.

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

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study, and should bring all unused and used study drug to each study visit. At the week 12 visit all unused and used study drug should be retained at the site and new study drug dispensed. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment it may be appropriate to withdraw the patient from the study (see Section 4.6). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

5.9. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3003. Eligibility criteria are set forth in that protocol.

5.10. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zolendronic acid	No prior use permitted
GnRH Analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	3 months (6 months for sustained 3-monthly injections)
Anti-Androgens	danazol	4 months
Anti-convulsant drugs (specified)	phenobarbital, carbamazepine, phenytoin, valproic acid, and primidone **Note**: All other anticonvulsants are allowed	1 month
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (6 months for depot subcutaneous or intramusclar injections)
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (6 months for depot subcutaneous or intramusclar injections)
Hormonal Contraceptives, contraceptive patches and vaginal rings	combined or progestin only Nuva Ring	1 month for patients reporting a typical (for them) menstrual period within < 2 months prior to the Screening Visit; otherwise 2 months
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	1 week

Drug Class	Examples	Window/Comments
Intrauterine Devices	levonorgestrel copper	2 months
Bone Agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	No prior use if used for reduced bone mineral density Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anti-Coagulants/ Platelets/Fibrinolytics	warfarin clopidogrel tranexamic acid vitamin k preparations factor Xa inhibitors	1 month
Glucocorticoids	prednisolone or prednisone dexamethasone	No window Anticipated use (at Screening) of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration ($\leq$ 21 days) higher dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein Inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir	2 weeks Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Drug Class	Examples	Window/Comments
Moderate and Strong P-glycoprotein Inhibitors	amiodarone atazanavir[f] azithromycin[a] captopril[b] carvedilol[g] clarithromycin[a] cobicistat[f] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	2 weeks (6 months for amiodarone) Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Abbreviation: GnRH, gonadotropin-releasing hormone
a. Roxithromycin is allowed
b. All other angiotensin converting enzyme inhibitors are allowed
c. Tacrolimus is allowed
d. Amlodipine and nifedipine are allowed
e. Fluconazole is allowed
f. Integrase inhibitors are allowed
g. Metoprolol and atenolol are permitted

5.10.2. Permitted Medications

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

5.10.2.1. Analgesics

From the Screening 1 visit to the Week 24 (or Early Termination) visit, the recommended analgesics for uterine-fibroid associated pain are as follows:

- First-line: ibuprofen
- Second-line: non-ibuprofen non-steroidal anti-inflammatory drug or acetaminophen
- Third-line: opioid or opioid-acetaminophen combination
- Fourth-line: investigator discretion

The purpose of these recommendations is to standardize, to the extent possible, analgesic medication use to facilitate the effects on the secondary endpoint regarding of uterine-fibroid-related pain.

Patients should be instructed not to use analgesics for prophylactic purposes.

5.10.2.2. Iron Therapy

Women with a hemoglobin < 8.0 g/dL are excluded from participating in the study. Women identified during the screening period to have a microcytic iron deficiency anemia defined as a hemoglobin ≥ 8 g/dL and ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must be started on iron therapy, either oral or parenteral and then continued on treatment during the study. Women who enter the screening period on iron therapy may continue iron treatment during the study. Women who develop new microcytic iron deficiency anemia during the study defined as a hemoglobin ≤ 10 g/dL, a mean corpuscular volume below the lower limit of normal, and a low serum iron and ferritin, must also be started on iron therapy, either oral or parenteral. 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 reported through the central lab.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of uterine fibroids and use of intrauterine devices are prohibited from the Screening 1 visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities in the study synopsis (see Section 1.1). Study procedures are briefly described within Section 6.8. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities 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, visual acuity assessment, 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
- Complete physical examination and visual acuity assessment
- 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, including TSH, 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 2 years 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 with an endometrial suction curette (eg, 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.

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 reported through the central lab. Please see Section 5.10.2.2 for guidance on iron therapy.

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 reported through the central lab. 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.

6.2.3. Screening 3 Visit

The patient will return for the Screening 3 visit if her menstrual blood loss from cycle 1 is ≥ 80 mL and within ≤ 15 days after the Screening 2 visit. At the Screening 3 visit, review of inclusion and exclusion criteria will be conducted to confirm continued eligibility. Concomitant medication and adverse events will be assessed and vital signs taken. A signs and symptoms directed physical examination, a 12-lead ECG and a urine pregnancy test will be performed. At this visit, review the endometrial biopsy results and review mammogram results, if available.

Confirm that the bone densitometry scans have been submitted for central reading. The mammogram and central bone densitometry results must be available prior to randomization.

6.2.4. Screening 4 Visit

The Screening 4 visit should be skipped if the menstrual blood loss is ≥ 160 mL in the first screening cycle. If not skipped, then the Screening 4 visit is scheduled to occur within 5 (+2) days after cessation of the patient's menses following Screening 3 visit. At the Screening 4 visit, the patient's feminine products will be 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.

6.2.5. Menstrual Blood Loss Repeat Collection

At the discretion of the investigator, the collection of menstrual blood loss can be repeated once during the screening period (either after the first or second screening cycle) 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.

6.2.6. Re-Screening

Patients who fail screening may be re-screened with approval of the medical monitor. Patients undergoing re-screening will sign a new informed consent form and issued a new screening number. For patients who begin re-screening within 10 weeks of signing the original informed consent form, transvaginal ultrasound, endometrial biopsy, and bone densitometry do not need to be repeated, if performed previously.

6.2.7. Retesting

Screening laboratory tests may be repeated once during the Screening period, if necessary, at the investigator's discretion. For laboratory-based entry criteria, the most recent value will be used to determine eligibility. Additional laboratory retesting requires the approval of the medical monitor. Retesting of other procedures (except once, as required, due to technical or logistical issues such as an inadequate sample) also require approval of the medical monitor.

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, waist circumference, ECGs, clinical laboratory tests, pregnancy tests, and adverse event collection will occur at each visit. Bone densitometry will occur at the Week 12

and Week 24 visits. A repeat transvaginal ultrasound (with or without a transabdominal ultrasound) will be performed at the Week 24 visit. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound). The endometrial biopsy will be read centrally. 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/pharmacodynamic sampling on visits at which these specimens are drawn. Patients must come to the clinic in the fasted state (eg, nothing to eat or drink other than water after midnight the day before the clinic visit) for the Baseline Day 1 and Week 24/Early Termination visits.

For visits *other than* Baseline Day 1 and Week 24/Early Termination, if the clinic visit cannot be scheduled for the morning, patients may eat in the morning but should not have eaten or had anything to drink other than water, coffee, or tea for at least 2 hours prior to the clinic visit and must not eat or drink (other than water, coffee or tea) for at least 1 hour after the clinic visit. In these situations, the laboratory requisitions must indicate that the patient was not fasted for their chemistry and lipid testing.

6.4. Continuation into Extension Study

It is expected that most patients will enter the 28-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. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the following procedures do not need to be performed: transvaginal ultrasound (with or without a transabdominal ultrasound), endometrial biopsy, and bone densitometry. These procedures may be performed, however, at the investigator's discretion, if they aid in follow-up of ongoing adverse events.

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 prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, 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 investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first. Refer to the Schedule of

Activities at the end of the synopsis (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.6. Additional Safety Follow-Up Procedures

For patients not continuing into the extension study (MVT-601-3003), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits.

- 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.
- Patients with endometrial biopsy findings of endometrial hyperplasia or endometrial cancer on the endometrial biopsy at the Week 24/Early Termination visit will undergo a repeat biopsy in 3 to 6 months after the Week 24/Early Termination and will be contacted to obtain information on procedures performed or treatments received (if any) for the biopsy findings through the time of the repeat biopsy. The repeat biopsy will be submitted to the central laboratory. In addition, patients with endometrial hyperplasia with atypia will be evaluated and managed, as needed, by a gynecologist.
- Patients who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit relative to baseline will undergo a follow-up DXA scan 6 months (± 1 month) after discontinuation of study drug and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat DXA scan. The follow-up DXA scan will be submitted for central reading.

6.7. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, PK and pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, etc. may be conducted as needed. See Schedule of Events (Section 1.1) for tests that may be performed if indicated at an unscheduled visit. Consult with the medical monitor, if needed, to discuss Unscheduled visit testing.

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 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.

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).

Queries will be handled by the vendor managing the eDiary data through the clinical site. The eDiary data will be reviewed by the study staff.

Patients will also receive a paper diary to enter information on menstruation status and feminine product use starting with Screening 1 visit and ending when they receive their eDiary at the Screening 3 visit.

6.8.1.6. 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. With exception of Baseline Day 1 (see Section 1.1), patients will complete the MIQ at each visit at the site before other study procedures.

6.8.1.7. Uterine Fibroid Symptom – Quality of Life

The Uterine Fibroid Symptom and Health-Related 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. With the exception of Baseline Day 1 (see Section 1.1), patients will complete the UFS-QOL before other study procedures.

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

The European Quality of Life Five-Dimension Five-Level Scale (EQ-5D-5L) 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 5-point categorical scales ranging from "no problem" to "severe problem."

Patients will complete the EQ-5D-5L questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit. With the exception of Baseline Day 1 (see Section 1.1), patients will complete EQ-5D-5L before other study procedures.

6.8.1.9. Patient Global Assessment for Symptoms and Patient Global Assessment for Function

These simple questions are used by the patient to qualitatively describe severity of symptoms or effects on function (PGA) (see Appendix 6) on a schedule described in the Schedule of Activities (see Section 1.1). With the exception of Baseline Day 1 (see Section 1.1), patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site on a schedule described in the Schedule of Activities (see Section 1.1). With the exception of Baseline Day 1, patients will answer these questions before other types of study procedures. The PGA for function and PGA for symptoms will be completed on a paper questionnaire at the study site.

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.

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.

Table 6-1 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Hemoglobin A1c Creatine Kinase Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase	White Blood Cell (WBC) Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and Clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine Microscopy
	Lipids	**Pregnancy**
	Total Cholesterol Low Density Lipoprotein High Density Lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)
Hormones	**Serology**	**Iron Studies**
Thyroid-Stimulating Hormone Prolactin Luteinizing Hormone Follicle-Stimulating Hormone Estradiol Progesterone Vitamin D [25(OH)D]	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody	Iron Ferritin

A separate sample will be collected at the Day 1 visit in all patients and will be banked for hepatitis serology (Table 6-1). The samples will be analyzed, if requested, by the medical monitor for evaluation of abnormal liver tests during the study.

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, serology, and plasma and serum hormone levels. Each study site will conduct urine pregnancy tests locally. If the hemoglobin is $\leq$ 10 g/dL and mean corpuscular volume is below the lower limit of normal, a ferritin and iron level will be reported through the central lab.

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

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

6.8.2.5. Electrocardiograms

ECGs (12-lead) will be obtained at the Screening 3 visit, the Baseline Day 1 visit, the Week 12 visit, and at the Week 24 or early withdrawal and Follow-up visits, as well as if needed to evaluate any signs or symptoms. ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.8.2.6. Endometrial Biopsy

An endometrial biopsy will be obtained using an endometrial suction curette (eg, Pipelle) and submitted to the central laboratory for reading. If the biopsy is inadequate for diagnosis at either Screening or at Week 24, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate for diagnosis at Screening, the patient is not eligible for the study. Endometrial biopsy will be performed at the Week 24 visit only if indicated (endometrial thickness at any location is ≥ 4 mm or if any other endometrial abnormality is visualized on the Week 24 ultrasound).

6.8.2.7. Bone Mineral Density

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

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. A central core imaging laboratory will collect and evaluate all DXA scans for acceptability, and will have bone mineral density assessed as per the imaging charter. Data from the DXA scans will be managed and analyzed separately by the core laboratory and integrated into the study's database at the end of the study. Bone mineral density changes for individual patient will be monitored by a central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the anatomical sites assessed during the study. In this case, it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for DXA scanning will be provided in the Study Reference Manual.

Please see Section 6.6 for follow-up of patients who are not continuing into the extension study (MVT-601-3003) and whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit relative to Baseline.

6.8.2.8. Visual Acuity

Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn at subsequent visual testing, as possible. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details).

Patients whose presenting visual acuity score is 90 or lower at the Baseline visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history.

Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from Baseline should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

6.8.3. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples of blood collected for pharmacogenomics testing (see Section 6.8.1.11) will be stored frozen at an appropriate vendor facility identified by the sponsor.

The need to conduct pharmacogenomic analysis may be identified after this study (or additional studies) has been completed. For this reason, the collected samples will be retained for up to 10 years after the last patient completes the study. A patient may request the destruction of her sample at any time. The sponsor may destroy the samples sooner than 10 years after the study completes.

7. SAFETY CONSIDERATIONS

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

7.1. Adverse Event Definitions

7.1.1. Adverse Event

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

Events meeting the definition of an adverse event **include**:

- A worsening, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition;
- Development of an intercurrent illness during the study;
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product;
- Injury or accidents: If a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (eg, for a fall secondary to dizziness, both "dizziness" and "fall" should be recorded separately); and
- An investigational abnormality (eg, laboratory parameter, vital sign, ECG) only if the abnormality is considered clinically significant by the investigator based on at least one of the following criteria:
    - Induces clinical signs or symptoms;
    - Requires active intervention;
    - Requires interruption or discontinuation of study drug.

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

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

Adverse events that occur during the study should be evaluated by the investigator and graded according to Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are 'intermittent'. All other events are 'continuous'. Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below.

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 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 affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Study procedure-related adverse events will be collected from the signing of the informed consent form.

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.

With the exception of adverse events that are considered related to study screening procedures, (which are to be recorded as adverse events), events 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. For terms not specified with the CTCAE, the criteria in Table 7-1 should be used to determine the grade severity.

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

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

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

7.5. Adverse Events of Clinical Interest Reporting

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

Any ALT or AST elevation of this degree or greater occurring during the 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 7.

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

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

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

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

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

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

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

7.6. Serious Adverse Event Reporting

Using a Safety 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:

Send completed Safety Report Forms to QuintilesIMS:

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

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

- North/South America: PPD
- Regional toll-free phone and fax lines distributed separately. Please refer to Study Reference Manual.

The initial report should include:

- Study number (MVT-601-3002)
- 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.

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

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

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for 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 6.8.2 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, 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.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
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 Enzyme Increase 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.
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	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior	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.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	Monitoring and Withdrawal Criteria
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.	hypersensitivity, migraine with aura, porphyria, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment.	

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

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

8.2. Monitoring

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

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

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

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

A statistical analysis plan (SAP) will describe the detailed statistical methods and analyses for this study. The SAP will be prepared and finalized prior to unblinding of patients' study treatment assignments.

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

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

9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and
- Mean screening menstrual blood loss using alkaline hematin method: < 225 mL versus ≥ 225 mL.

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

9.2. Analysis Populations

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

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

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

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

9.3. Efficacy Analyses

Inferential efficacy assessments will be made between the following groups and 24 Weeks of placebo:

- Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate;
- Relugolix Group B: 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.

Descriptive characterization of treatment effect will be assessed between both relugolix groups.

9.3.1. Primary Endpoint Analysis

The primary endpoint is the proportion of women in the relugolix Group A versus the placebo Group C who achieve both a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline in menstrual blood loss volume over the last 35 days of treatment as measured by the alkaline hematin method.

Baseline menstrual blood loss is defined as the average menstrual blood loss from the two Screening menstrual cycles used to meet the inclusion criteria prior to the date of the first dose of study drug as assessed by the alkaline hematin method. The menstrual blood loss during the final study month is the total menstrual blood loss during the last 35 days on treatment as assessed by the alkaline hematin method. The treatment comparison between the relugolix Group A and the placebo Group C will be analyzed using a Cochran-Mantel-Haenszel test statistic for stratified proportions. The differences between the relugolix Group A and placebo Group C and 2-sided 95% confidence intervals will be estimated based on stratum-adjusted Mantel-Haenszel proportions.

Patients who discontinue the study before Week 4 (28 days) will be considered as treatment failures for the primary endpoint. The primary analyses will be based on the ITT Population. In addition, analyses of the Per-Protocol Population will be used to support the primary efficacy analysis. Details will be provided in the SAP. Additional missing data imputations will be conducted as sensitivity analyses to support the primary analysis. Details will be provided in the SAP.

For the assessment of the superiority of relugolix Group A versus placebo Group C in the 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, a sample size of ~130 patients in the relugolix Group A versus ~130 in the placebo Group C will provide greater than 99% power to detect a difference of greater than 30% using a 2-sided test at

significance level of 0.05. The study will enroll 3 groups with a targeted 130 patients in each group for a total sample size of 390.

9.3.2. Secondary Endpoint Analyses

The secondary endpoints are listed below:

- Proportion of women in the relugolix Group B versus the placebo Group C who achieve a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume over the last 35 days of treatment, as measured by the alkaline hematin method.

The following secondary endpoints will be assessed comparing each relugolix treatment group to placebo inferentially and relugolix Group A to Group B descriptively:

- Time to achieving a menstrual blood loss volume of < 80 mL AND at least a 50% reduction from baseline menstrual blood loss volume as measured by the alkaline hematin method;
- Change from Baseline to Week 24 in menstrual blood loss;
- Proportion of women who achieve amenorrhea over the last 35 days of treatment;
- 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 impact of uterine fibroids based on the UFS-QOL activities domain;
- Change from Baseline to Week 24 in the interference of uterine fibroids with physical activities based on UFS-QOL Question 11;
- Change from Baseline to Week 24 in the interference of uterine fibroids with social activities based on UFS-QOL Question 20;
- Change from Baseline to Week 24 in embarrassment caused by uterine fibroids based on UFS-QOL Question 29;
- Change from Baseline to Week 24 in uterine fibroid-related symptoms based on the Uterine Fibroid Scale – Symptom Severity;
- Change from Baseline to Week 24 in uterine fibroid-related quality of life based on the Uterine Fibroid Scale – Health-related Quality of Life;
- Change in PGA for uterine fibroid related function from Baseline to Week 24;
- Change in PGA for uterine fibroid symptoms from Baseline to 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, 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, UFS-QOL score, PGA for function and symptoms, MIQ Score, 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.

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 the randomized study drug treatment through approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for uterine fibroids, or the date and time of the first dose of open-label extension (MVT-601-3003) study drug, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

The severity of all adverse events is to be evaluated by the investigator based on the National Cancer Institute's CTCAE. All adverse events will be coded to preferred term and system organ

class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the 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.

ECGs will 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 will be determined by the central radiology laboratory at the femoral neck, lumbar spine (L1-L4), and total hip. Values at Baseline, Week 12, and Week 24 visits will be summarized by treatment group along with the absolute and percent changes from Baseline and associated 95% confidence intervals. The number and percentage of patients meeting a bone mineral density decline of at least 7% by body area (lumbar, total hip, and femoral neck) will be presented with 95% confidence intervals by treatment group.

To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3001 and MVT-601-3002) with a formal comparison of Group A versus Group B (see details in the joint statistical analysis plan).

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

9.5. Pharmacokinetic and Pharmacodynamic Analyses

The PK concentration data (relugolix, estradiol [PK lab], and norethindrone) and serum pharmacodynamic data (LH, FSH, estradiol [central lab] and progesterone) will be listed and summarized descriptively by treatment arm and visit.

Plasma relugolix PK data will be combined with data from other phase 1 and phase 2 studies for population PK analysis. Full details will be provided in a separate Population PK SAP and reported separately. Plasma PK parameters of relugolix will be derived and summarized. The relationship between efficacy, safety, and exposure will be explored.

9.6. Exploratory Analyses

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

- 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.

9.7. Interim Analyses

There are no planned interim efficacy analyses.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for one year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed

consent) will be submitted by the investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

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

10.1.3. Informed Consent

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

10.1.4. Confidentiality

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

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

10.1.5. Study Committees and Communication

There will be two formal committees for this study, a Steering Committee and a Data and Safety Monitoring Board.

The study will be overseen by a Steering Committee consisting of experts in the field of Women's Health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study. Steering Committee members will remain blinded to patients' treatment assignment and all unblinded data until the database is officially locked and unblinded.

An independent Data and Safety Monitoring Board will be established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee will evaluate the safety of study participants on an ongoing basis. Further details on the composition and responsibility of the Data and Safety Monitoring Board will be outlined in a separate charter.

10.1.6. Study Files and Retention of Records

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

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

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

Clinical study documentation includes the IB, signed protocol and amendments, signed informed consents, notification of serious adverse events and related reports, any dispensing and accountability logs, shipping records of investigational product and study-related materials, documentation of financial aspects of the study, insurance statement, and signed agreement between the involved parties, dated and documented IRB/IEC approval, approval of regulatory

authorities as applicable, decoding procedures for blinded studies, curriculum vitae and all training records of study site personnel, and all correspondence pertaining to the conduct of the study.

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

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

10.1.7. Electronic Case Report Forms

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

10.1.8. Investigational Product Accountability

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

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

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

10.1.9. Inspections

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

10.1.10. Protocol Compliance

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

10.2. Sponsor Responsibilities

10.2.1. Protocol Modifications

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

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

10.2.2. Study Report

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

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

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

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

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

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

10.3.2. Access to Information for Auditing or Inspections

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

10.3.3. Study Discontinuation

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

10.3.4. Publications

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

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

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

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

REFERENCES

ACOG Practice Bulletin No. 96: Alternatives to Hysterectomy in the Management of Leiomyomas. Obstetrics & Gynecology 2008;112(2 Part 1):387-400.

Activella FDA Clinical Pharmacology Review. November 1998. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20907.cfm. Accessed: 16 August 2016.

Activella US Prescribing Information. Revised 10/2013. Available at: http://www.novo-pi.com/activella.pdf. Accessed: 06 August 2016.

Archer DF, Chwalisz K, Feldman R, Stewart EA, Lukes AS, North J, Gao J, Williams LA, Jain R. Elagolix for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UF): Results from a phase 2A proof-of-concept study. American Society for Reproductive Medicine (Oct 17-21). October 20, 2015. Abstract O-181, available at: http://www.fertstert.org/article/S0015-0282(15)00717-7/pdf. Accessed: 08 July 2016.

Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. American Journal of Obstetrics and Gynecology 1992;166(2):740-5.

Cardozo ER. The estimated annual cost of uterine leiomyomata in the United States. American Journal of Obstetrics and Gynecology 2012;206(3):0092-0100.

Carr BR, Marshburn PB, Weatherall PT, Bradshaw KD, Breslau NA, Byrd W, Roark M, Steinkampf MP. An evaluation of the effect of gonadotropin-releasing hormone analogs and medroxyprogesterone acetate on uterine leiomyomata volume by magnetic resonance imaging: a prospective, randomized, double blind, placebo-controlled, crossover trial. Journal of Clinical Endocrinology & Metabolism 1993;76(5):1217-23.

Chwalisz K, Surrey E, Stanczyk FZ. The hormonal profile of norethindrone acetate: rationale for add-back therapy with gonadotropin-releasing hormone agonists in women with endometriosis. Reproductive Sciences 2012;19(6):563-71.

Food and Drug Administration (FDA). Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation. US Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. July2009.

Franke HR, van de Weijer PHM, Pennings TMM, van der Mooren MJ. Gonadotropin-releasing hormone agonist plus add-back' hormone replacement therapy for treatment of endometriosis: a prospective, randomized, placebo-controlled, double-blind trial. Fertility and Sterility 2000;74(3):534-539. Available at: http://www.fertstert.org/article/S0015-0282(00)00690-7/pdf. Accessed: 16 August 2016.

Gliklich RE, Leavy MB, Velentgas P, Campion DM, Mohr P, Sabharwal R, Whicher D, Myers ER, Nicholson WK. Identification of Future Research Needs in the Comparative Management of Uterine Fibroid Disease. A Report on the Priority-Setting Process, Preliminary Data Analysis, and Research Plan. Effective Healthcare Research Report No. 31. (Prepared by the Outcome DEcIDE Center, under Contract No. HHSA 290-2005-0035-I, TO5). AHRQ Publication No. 11- EHC023-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011. Available at: http://effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed: 16 August 2016.

Hallberg L, Nilsson L. Determination of menstrual blood loss. Scand J Clin Lab Invest. 1964;16(2):244–248.

Hapangama DK, Bulmer Judith N. Pathophysiology of heavy menstrual bleeding. Women's health 2016;12(1):3-13.

Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide Acetate Depot and Hormonal Add-Back in Endometriosis: A 12-Month Study. Obstetrics & Gynecology 1998;91(1):16-24.

Lee DY, Park HG, Yoon BKoo, Choi D. Effects of different add-back regimens on hypoestrogenic problems by postoperative gonadotropin-releasing hormone agonist treatment in endometriosis. Obstetrics & gynecology science 2016;59(1):32-8. Available at: http://synapse.koreamed.org/Synapse/Data/PDFData/3021OGS/ogs-59-32.pdf. Accessed: 16 August 2016.

Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2006;(2):CD003855.

Marret H, Fritel X, Ouldamer L, Bendifallah S, Brun J.L, De Jesus I, Derrien J, Giraudet G, Kahn V, Koskas M, Legendre G, Lucot J.P, Niro J, Panel P, Pelage J.P, Fernandez H. Therapeutic management of uterine fibroid tumors: updated French guidelines. European Journal of Obstetrics and Gynecology 2012;165(2):156-164.

Morris EP, Rymer J, Robinson J, Fogelman I. Efficacy of tibolone as add-back therapy' in conjunction with a gonadotropin-releasing hormone analogue in the treatment of uterine fibroids. Fertility and Sterility 2008;89(2):421-428.

Simpson PD, McLaren JS, Rymer J, Morris EP. Minimising menopausal side effects whilst treating endometriosis and fibroids. Post Reproductive Health: The Journal of the British Menopause Society. 2015;21(1):16-23.

Stewart EA. Clinical Practice. Uterine Fibroids. N Engl J Med. 2015;372(17):1646-55.

Wu D, Hu M, Hong L, Hong S, Ding W, Min J, Fang G, Guo W. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. Archives of Gynecology and Obstetrics 2014;290(3):513-523.

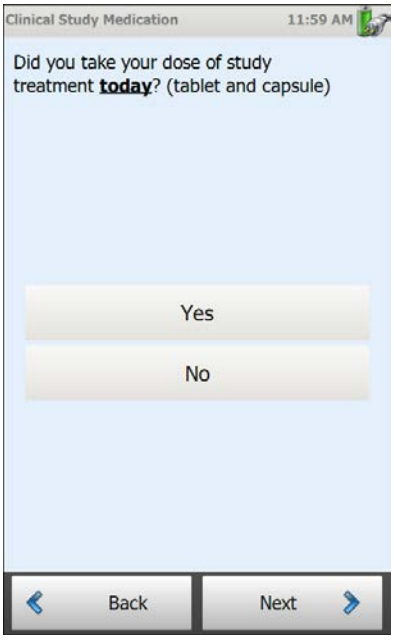
Zupi E, Marconi D, Sbracia M, Zullo F, De Vivo B, Exacustos C, Sorrenti G. Add-back therapy in the treatment of endometriosis-associated pain. Fertility and Sterility 2004;82(5):1303-1308.

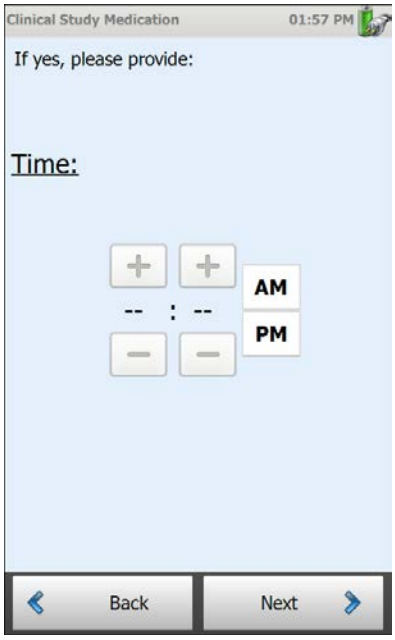
APPENDICES

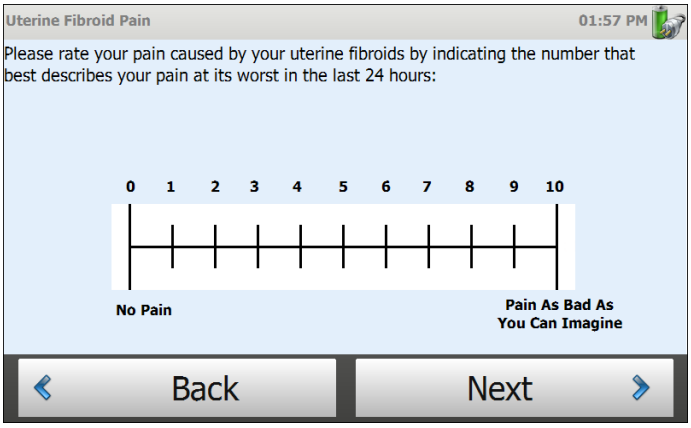
Appendix 1. Breast Imaging Reporting and Data System (BI-RADS)

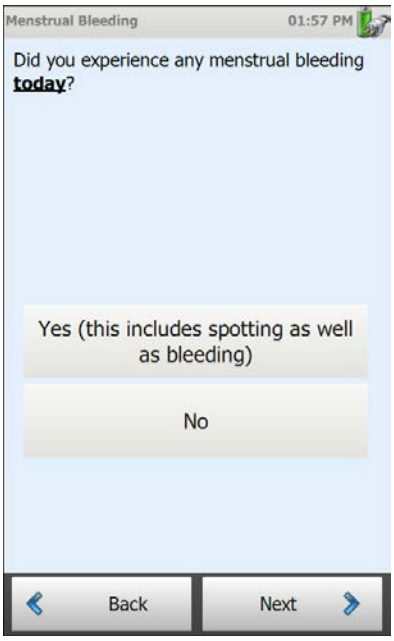
Category	Assessment	Follow-up
0	Need additional imaging evaluation: means that more studies are necessary to gather more information.	Additional imaging needed before a category can be assigned.
1	Negative: means that there is no significant or noticeable abnormality to report.	Continue annual screening mammography (for women over age 40).
2	Benign (noncancerous) finding: means that there has been a finding, such as benign calcifications or fibroadenoma, which is not cancerous.	Continue annual screening mammography (for women over age 40).
3	Probably benign: means that there is a finding that is most likely benign, but should be followed in a shorter period of time to see if the area of concern changes.	Receive a 6-month follow-up mammogram.
4	Suspicious abnormality: means that there are suspicious findings that could turn out to be cancer.	May require biopsy.
5	Highly suggestive of malignancy (cancer): means that there are findings that look like and probably are cancer.	Requires biopsy.
6	Known biopsy-proven malignancy (cancer): means that any findings on the mammogram have already proven to be cancer through a biopsy.	Biopsy confirms presence of cancer before treatment begins.

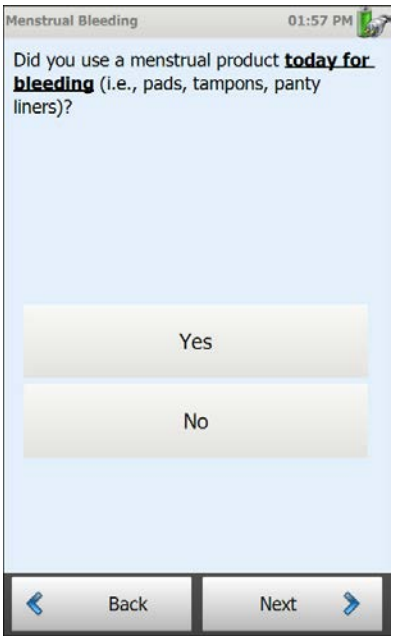
Appendix 2. Daily eDiary

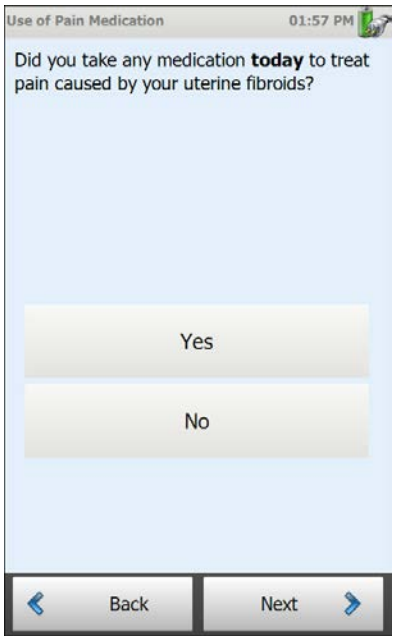


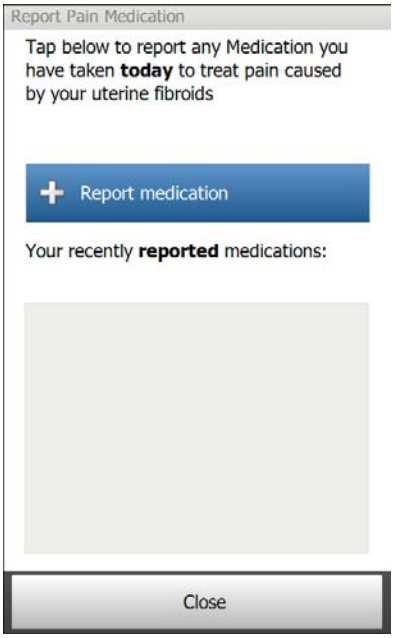


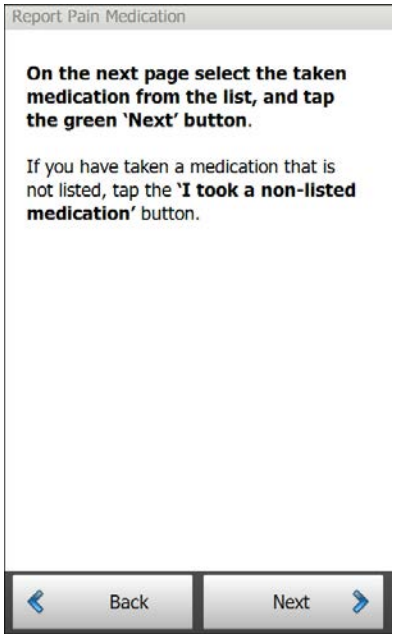


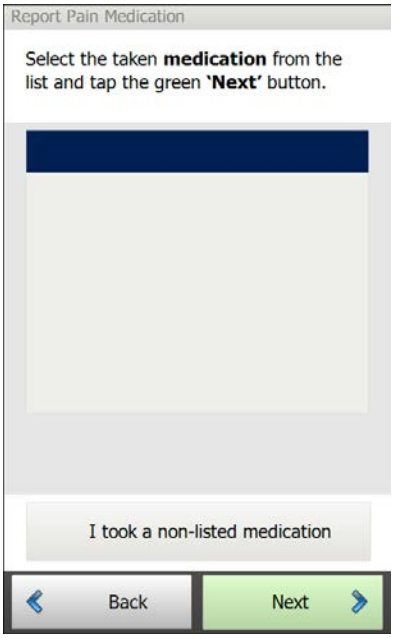

Menstrual Bleeding
01:57 PM
Did you experience any menstrual bleeding **today**?
Yes (this includes spotting as well as bleeding)
No
Back
Next

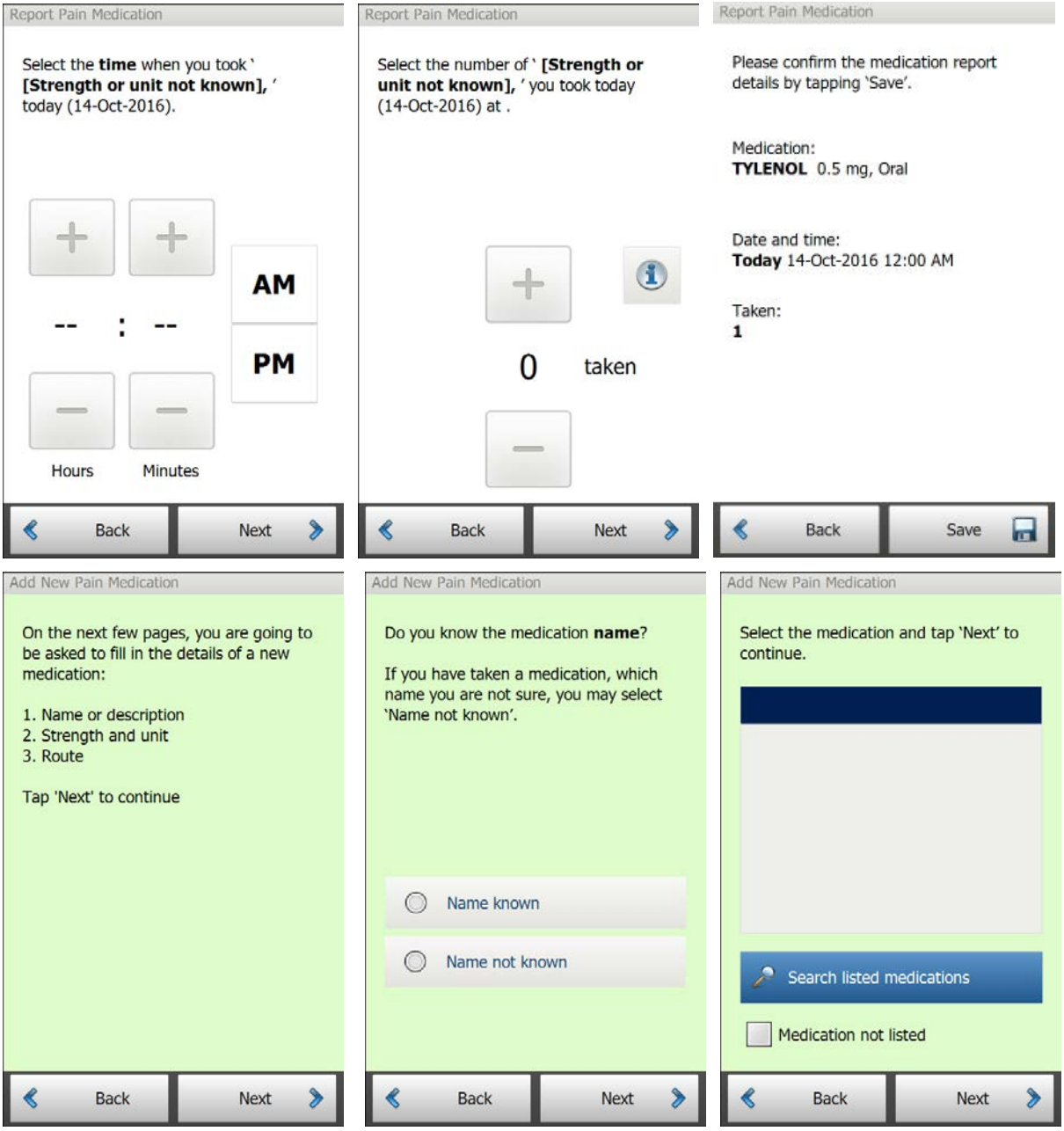

Menstrual Bleeding
01:57 PM
Did you use a menstrual product **today for bleeding** (i.e., pads, tampons, panty liners)?
Yes
No
Back
Next


Use of Pain Medication
01:57 PM
Did you take any medication **today** to treat pain caused by your uterine fibroids?
Yes
No
Back
Next


Report Pain Medication
Tap below to report any Medication you have taken **today** to treat pain caused by your uterine fibroids
Report medication
Your recently **reported** medications:
Close

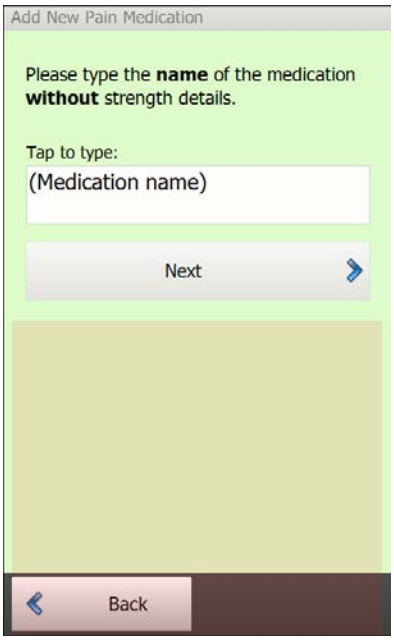

Report Pain Medication
On the next page select the taken medication from the list, and tap the green 'Next' button.
If you have taken a medication that is not listed, tap the **'I took a non-listed medication'** button.
Back
Next

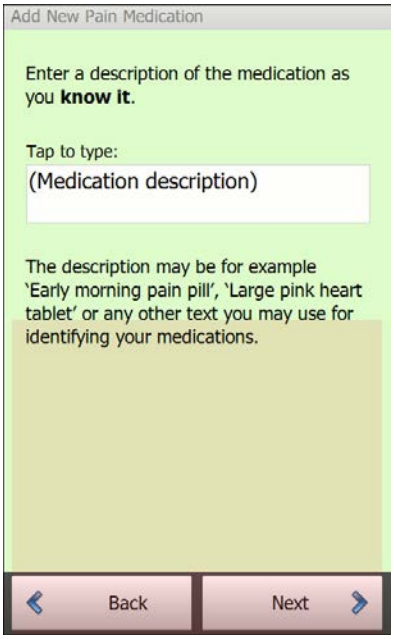

Report Pain Medication
Select the taken **medication** from the list and tap the green **'Next'** button.
I took a non-listed medication
Back
Next

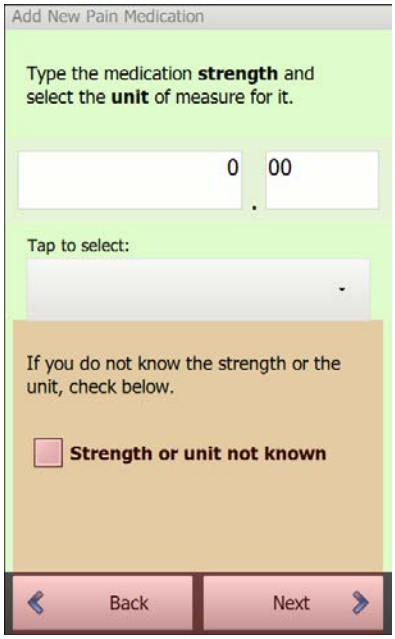

Report Pain Medication
Select the time when you took ' [Strength or unit not known], ' today (14-Oct-2016).
AM
PM
-- : --
Hours
Minutes
Back
Next
Report Pain Medication
Select the number of ' [Strength or unit not known], ' you took today (14-Oct-2016) at .
0 taken
Back
Next
Report Pain Medication
Please confirm the medication report details by tapping 'Save'.
Medication:
TYLENOL 0.5 mg, Oral
Date and time:
Today 14-Oct-2016 12:00 AM
Taken:
1
Back
Save
Add New Pain Medication
On the next few pages, you are going to be asked to fill in the details of a new medication:
1. Name or description
2. Strength and unit
3. Route
Tap 'Next' to continue
Back
Next
Add New Pain Medication
Do you know the medication name?
If you have taken a medication, which name you are not sure, you may select 'Name not known'.
Name known
Name not known
Back
Next
Add New Pain Medication
Select the medication and tap 'Next' to continue.
Search listed medications
Medication not listed
Back
Next

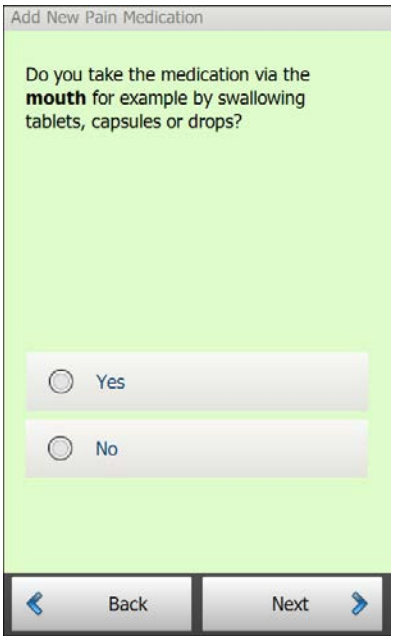

Add New Pain Medication
Enter the first few characters of the medication and tap 'Search'.
Tap to type:
(First characters)
Search
View all medications
Back


Add New Pain Medication
Select the medication and tap 'Next' to continue.
Medication not listed
Back
Next

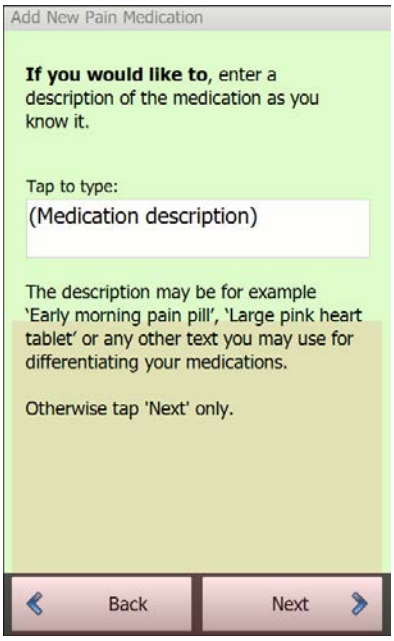

Add New Pain Medication
Please type the name of the medication without strength details.
Tap to type:
(Medication name)
Next
Back

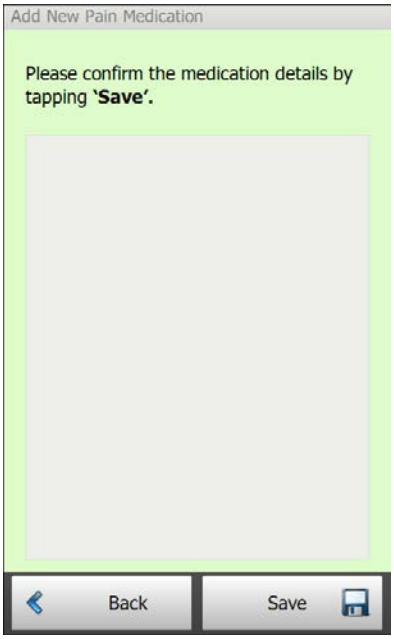

Add New Pain Medication
Enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for identifying your medications.
Back
Next

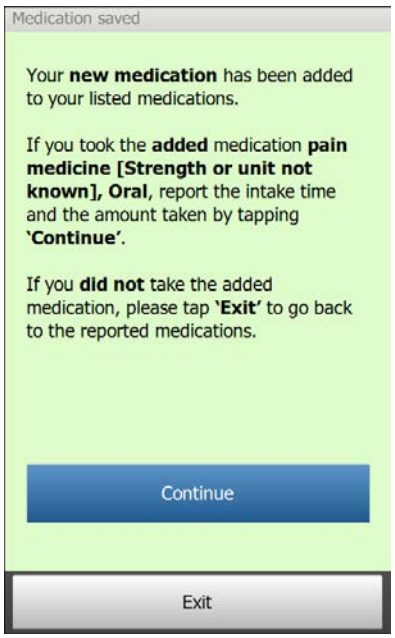

Add New Pain Medication
Type the medication strength and select the unit of measure for it.
0
00
Tap to select:
If you do not know the strength or the unit, check below.
Strength or unit not known
Back
Next


Add New Pain Medication
Do you take the medication via the **mouth** for example by swallowing tablets, capsules or drops?
Yes
No
Back
Next


Add New Pain Medication
Select the **route** for the medication:
Back
Next


Add New Pain Medication
If you would like to, enter a description of the medication as you know it.
Tap to type:
(Medication description)
The description may be for example 'Early morning pain pill', 'Large pink heart tablet' or any other text you may use for differentiating your medications.
Otherwise tap 'Next' only.
Back
Next


Add New Pain Medication
Please confirm the medication details by tapping **'Save'.**
Back
Save


Medication saved
Your **new medication** has been added to your listed medications.
If you took the **added** medication **pain medicine [Strength or unit not known], Oral**, report the intake time and the amount taken by tapping **'Continue'**.
If you **did not** take the added medication, please tap **'Exit'** to go back to the reported medications.
Continue
Exit

Appendix 3. Menorrhagia Impact Questionnaire

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

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

MIQ, Menorrhagia Impact Questionnaire.

Appendix 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

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

f:\institut\cultedep\project\hc1617\question\original\final\uterq.doc-21/12/2001

2

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

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 ❑

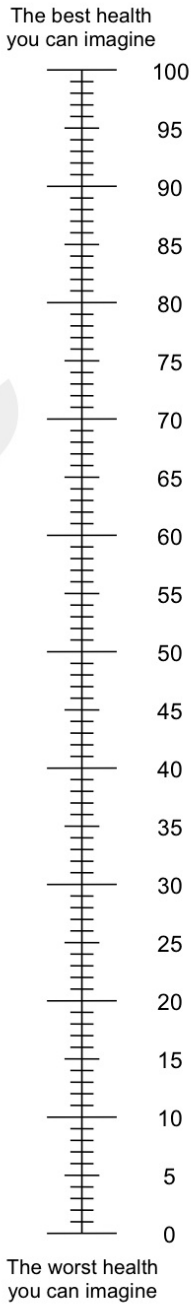
ANXIETY / DEPRESSION

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 ❑

2

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

YOUR HEALTH TODAY = ☐



Appendix 6. Patient Global Assessments

Patient Global Assessment (for function)

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

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

Patient Global Assessment (for symptoms)

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

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

Appendix 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.

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.