Clinical Study Protocol

Protocol Title:	A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy
Protocol Number:	MVT-601-050
Amendment Number:	4
Compound:	Relugolix Combination Therapy (relugolix, estradiol, norethindrone acetate)
Study Phase:	Phase 3
Short Title:	A Phase 3 Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis who are at Risk for Pregnancy
Sponsor Name:	Myovant Sciences GmbH Aeschengraben 27 4051 Basel Switzerland
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CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy

Protocol Number: MVT-601-050 Amendment 4

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

[redacted]

22-Dec-2022 | 11:57 AM PST

Date

22-Dec-2022 | 2:33 PM PST

Date

22-Dec-2022 | 12:51 PM PST

Date

22-Dec-2022 | 11:58 AM PST

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)	Principal Investigator Signature
Clinical Site Number	Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy

Short Title: A Phase 3 Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Fibroids or Endometriosis Who Are at Risk for Pregnancy

Protocol Number: MVT-601-050

Location: North America

Study Centers: Approximately 130 sites

Study Phase: Phase 3

Target Population: Women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy

Rationale:

This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy. Myovant is developing relugolix combination therapy for the indications of the management of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis. Both conditions are prevalent in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy of relugolix combination therapy in treatment of symptoms associated with endometriosis or uterine fibroids, or the safety of patients undergoing treatment with relugolix combination therapy. By quantifying the contraceptive effectiveness of relugolix combination therapy (using the Pearl Index [PI]), results from this study will provide evidence for patients and their healthcare providers to make an informed decision about the need to use additional nonhormonal contraception while being treated with relugolix combination therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: $PI = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy:	
Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
"Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
"Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
Contraceptive efficacy in various populations and analysis sets.	Cumulative 1-year pregnancy rates.
Safety	
To describe the safety of relugolix combination therapy.	Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
To evaluate change in bone mineral density during treatment with relugolix combination therapy.	Percent change in bone mineral density from baseline to 6 and 12 months on-treatment at lumbar spine (L1-L4), total hip, and femoral neck.

Objectives	Endpoints
To evaluate post-treatment change in bone mineral density.	Percent change from baseline and 12 months on-treatment (or Early Termination) to the 6-month and 12-month post-treatment time points at lumbar spine (L1-L4), total hip, and femoral neck.
To estimate discontinuation rate.	Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

Overall Design:

Study MVT-601-050 is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy (relugolix 40 mg, estradiol [E2] 1 mg, and norethindrone acetate [NETA] 0.5 mg). Approximately 1020 sexually active women with uterine fibroids or endometriosis who are 18 to 50 years of age and will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

The study period consists of a Screening Period (Visit 1), a 52-week Treatment Period (Visits 2 to 6), a 14-day post-treatment Safety Follow-Up Period (Visit 7), as well as a 12-month Post-Treatment Follow-Up (PTFU) period during which bone mineral density (BMD) is monitored.

Participant eligibility will be determined based on assessments performed at Visit 1. The participant's medical and gynecological history (including contraception and use of prior medications) will be reviewed and a diagnosis of either uterine fibroids with heavy menstrual bleeding or endometriosis with associated pain will be confirmed (see inclusion criteria). An ultrasound may be performed to confirm diagnosis of uterine fibroids if there is no previous documented record from the past two years. Height, weight, and vital signs will be measured; and physical, gynecological, and breast examinations will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (βhCG) to rule out pregnancy, and participants will be screened for the sexually transmitted diseases (STDs) gonorrhea and chlamydia. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening for suicidal ideation will be performed using the Columbia – Suicide Severity Rating Scale (C-SSRS). Participants who are 40 or older will need to undergo a screening mammogram (see Appendix 7).

Participants who meet all eligibility criteria will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Prior to initiation of treatment with relugolix combination therapy on Day 1 (Visit 2), patients will need to undergo a baseline assessment of bone mineral density via dual-energy X-ray absorptiometry (DXA) scan. On Day 1 (Visit 2), continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable

updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. Participants must have a negative urine pregnancy test. Participants will also receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Finally, study medication will be dispensed, together with instructions for administration and back-up contraception, if applicable. The window for initiating dosing with relugolix combination therapy also depends upon contraceptive status. If Visit 2 occurs within the correct window, dosing may begin at Visit 2. Otherwise, the participant will initiate dosing at home when the appropriate window is reached and after another negative urine pregnancy test result is recorded in the eDiary. Thereafter, continuous treatment with relugolix combination therapy will be taken for 13 consecutive 28-day treatment cycles.

Throughout the Treatment Period, compliance with study intervention administration will be recorded daily in the eDiary. At the completion of each 28-day treatment cycle, the participant will record the results of a urine pregnancy test and indicate whether intercourse or use of additional contraception occurred during the previous 28-day treatment cycle. Each treatment cycle starts with the result of a home pregnancy test, the result of which must be negative and must be entered in the eDiary for a participant to continue in the study. Assessments of safety (physical, gynecological, and breast examinations; laboratory assessments; vital signs, etc.) will be performed throughout the study. DXA scans will be performed at 6-month intervals during treatment and the post-treatment follow-up period. Telephone visits to assess compliance and safety will be performed approximately 6 weeks following each on-site visit during the treatment period.

Fourteen days after discontinuation of treatment, a follow-up/end-of-treatment (EOT) visit (Visit 7) will be conducted. All assessments done at on-treatment visits will be repeated and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for selected serum chemistry assessments, including βhCG to determine pregnancy and safety assessments will be performed. A 12-month on-treatment DXA will be performed no later than the time of this visit. A mammogram will be performed, if indicated. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

Two PTFU DXAs will be performed at 6 months and 12 months after the end-of-treatment visit. Clinical laboratory tests (25-OH vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphate) will be performed if bone mineral density loss meets pre-specified criteria. Any participant who has an on-treatment pregnancy will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Inclusion and Exclusion Criteria:

Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 50 years of age (inclusive);

3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a diagnosis of uterine fibroids or endometriosis meeting *either* of the below criteria:
    a. Diagnosis of uterine fibroids by confirmation of ultrasound performed in the last 2 years (submucosal fibroids > 50% intracavitary are excluded) and patient report of heavy menstrual bleeding affecting quality of life.

       Note: If an ultrasound report from the last 2 years cannot be located, the participant should undergo transvaginal ultrasound at the time of screening to confirm the presence of one or more uterine fibroids.

    b. Diagnosis of endometriosis and has had, prior to signing the informed consent form, surgical or direct visualization (laparoscopy or laparotomy) and/or histopathologic confirmation of endometriosis, and during the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and/or during non-menstrual portion of the cycle in the prior month;
6. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
7. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through end of treatment;
8. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
9. Has body mass index (BMI) ≥ 18 kg/m^2;
10. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:
    a. Vascular disease (eg, cerebrovascular disease, coronary artery disease, peripheral vascular disease);
    b. Women over 35 who smoke tobacco-containing products;

c. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation);

d. Inherited or acquired hypercoagulopathies, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant);

Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

   Note: The specific reasons for exclusion should be documented in the interactive web-response system (IWRS).

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Malabsorptive disease (including, but not limited to, inflammatory bowel disease and gastric bypass surgery);
11. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's

discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

12. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
13. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

14. Has a known history of infertility or subfertility (examples include but are not limited to prior ectopic pregnancy, prior surgery of fallopian tube, prior imaging or procedure suggesting non-patent fallopian tube, history of infertility workup or treatments);
15. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
16. Has abnormal cervical cytology or cervical biopsy in the last 18 months demonstrating:
    a. Cytology of high grade squamous intraepithelial lesion, atypical squamous cells, atypical glandular cells, or any other cytology or biopsy indicating possible or confirmed high-grade dysplasia (defined as cervical intraepithelial neoplasia [CIN] grade 2+, which includes CIN2, CIN3, adenocarcinoma in situ, and cancer) or malignancy in the genital tract
    b. Atypical squamous cells of undetermined significance or low grade squamous intraepithelial lesion cytology, unless:
        - Age < 25, or
        - Negative for high-risk human papillomavirus (HPV), or
        - Patient underwent a colposcopy after the pap smear and within 6 months of screening and there were no visible lesions *or* sampling was performed and there were no lesions showing CIN2+
    c. Positive high-risk HPV test in the setting of a normal pap smear, unless:
        - Age < 25, or
        - Patient underwent a colposcopy after the pap smear and within 6 months of screening and there were no visible lesions *or* sampling was performed and there were no lesions showing CIN2+

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial).

17. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, intermenstrual/bleeding between menstrual periods, bleeding from a cervical polyp, recurrent bleeding after intercourse);
18. Has a known submucosal fibroid (> 50% intracavitary);
19. Women with a diagnosis of endometriosis who have had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis.

Other Conditions/Disorders

20. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
21. Has known human immunodeficiency virus (HIV) infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
22. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
23. Has known BRCA mutation or other mutation associated with increased risk of breast cancer;
24. 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;
25. History of suicidal ideation or suicidal behavior, or confirmed "yes" to any question (with exception of non-suicidal self-injurious behavior, unless deemed as an unacceptable risk by the investigator) on the C-SSRS;
26. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants with major depression, posttraumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders (based on Diagnostic and Statistical Manual of Mental Disorders 5 [DSM-5] criteria) who have been unstable or not well controlled based on the investigator or mental health professional's judgement, 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 treatment period should not be enrolled;
27. Has a hepatic hemangioma, or has a history of cholestasis with prior estrogen use or during pregnancy;
28. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
29. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;

30. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

31. Has a known or suspected pregnancy;
32. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
33. Is breastfeeding or has breastfed in the last year.

At risk of bone loss or unable to be monitored for changes in bone density

34. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
35. Has a bone mineral density Z-score ≤ -2.0 at lumbar spine, femoral neck, or total hip during the screening period;
36. Screening 25-OH vitamin D level < 12 ng/mL (patients with vitamin D deficiency with levels 12-19 ng/mL are permitted if supplementing with vitamin D);

    Note: If patients fail screening because of vitamin D levels, they may begin supplementing with vitamin D at the discretion of the treating clinician and be re-screened eight weeks later.

37. Has a history of or currently has osteoporosis, or other metabolic bone disease, collagen vascular disease, chronic kidney disease (CKD) stage 3 or greater with glomerular filtration rate (GFR) < 60 mL/min/m^2 using Modification of Diet in Renal Disease (MDRD) method, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, hyperthyroidism, anorexia nervosa, abnormal bone mineral metabolism (eg, hypophosphatemia), or low traumatic (fragility) fracture. 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;
38. Past history of use or current use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
39. Prior use of depo-medroxyprogesterone acetate for a treatment period > 2 years.

Concomitant and Recent Medications/Devices

40. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
41. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;

42. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein).
43. Has used chronic glucocorticoids that are oral, parenteral, inhaled (prednisone equivalents of ≥ 2.5mg daily for ≥ 3 months) in 12 months prior to the study. Women with epidural or spinal glucocorticoid use at any dose in the last 12 months are excluded.

Miscellaneous

44. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

Disclosure Statement

This is a single arm, open-label study to evaluate the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy.

Number of Participants:

Approximately 1020 participants will be enrolled. The sample size has been set to attain at least 10,000 treatment cycles and 7000 at-risk treatment cycles for pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse) in participants 18 to 50 years of age at the time of enrollment (see Section 9.2). Additional participants may be enrolled to ensure a minimum of 200 participants completing the study. The enrollment aim is approximately 50% of participants with uterine fibroids (with a minimum of 40%), and approximately 50% of participants with endometriosis (with a minimum of 25%).

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study but do not participate in the study are not considered enrolled.

Intervention Groups and Duration:

Relugolix combination therapy (relugolix 40 mg, E2 1 mg, and NETA 0.5 mg) as a fixed-dose combination tablet is to be taken orally QD at approximately the same time each day. Relugolix combination therapy treatment is continuous; that is, a tablet is to be taken daily for the entire duration of the treatment period, without a drug-free interval.

Study intervention will be self-administered during 13 consecutive 28-day treatment periods ("Cycles"), for a total duration of 52 weeks.

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

Participants may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove participants from therapy under this protocol for reasons of safety and/or lack of compliance, as discussed below. Participants removed from study intervention for any reason will, if possible, undergo assessments for an early termination visit (see Schedule of Activities, Section 1.3), then return again approximately 14 days after the end of treatment (ie, after the participant's last dose of study intervention). If the patient has provided consent, she will be recommended to undergo PTFU BMD assessments with DXA and collection of blood samples for clinical laboratory tests at 6 and 12 months (if meeting prespecified criteria).

Criteria for Evaluation:

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the estimated date of delivery (EDD) will be ascertained. The estimated conception date (ECD) will be calculated as:

- EDD – 38 weeks = ECD

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses, or βhCG level.

Statistical Methods:

Contraceptive Efficacy

This study has one primary endpoint, the At-Risk PI, calculated on the basis of the number of on-treatment pregnancies in the numerator and the number of at-risk cycles of exposure in the denominator. The numerator and denominator are thus slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, the primary contraceptive efficacy analysis, will be conducted using a restricted intent-to-treat (rITT) population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred (ie, a treatment cycle containing an ECD for a pregnancy). The At-Risk PI will be presented together with the two-sided 95% confidence interval (CI) calculated based on a Poisson distribution (Benda et al. 2004). There is no hypothesis associated with the primary endpoint.

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% Cis with a Poisson distribution.

Safety

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of

treatment discontinuations due to adverse events, vital signs, laboratory evaluations, mammogram, and DXA scans.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention, and severity. An adverse event reported more than once for a participant will be counted once at the maximum severity or strongest relationship to study intervention when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Mammograms will be obtained at baseline and then at the end of treatment for women who are age 40 or older.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the baseline, 6- and 12-month on-treatment time points, as well as at 6-and 12-months post-treatment (hereafter referred to as PTFU Month 6 and PTFU Month 12). All patients who discontinue treatment prior to completing 13 cycles of study medication will still undergo PTFU Month 6 and PTFU Month 12 DXA assessments. The percent change in BMD will be measured at all time points relative to the baseline value.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

Sample Size Determination

Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 10,000 treatment cycles in participants 18 to 50 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of thirteen 28-day treatment cycles;
- 40% of participants will discontinue the study;
- Participants who discontinue will, on average, contribute 5 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% CI for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$, where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100 woman-years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% Cis meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with the FDA Guidance for Industry (FDA 2019).

Assuming 70% of menstrual cycles are at-risk and a 40% dropout rate (assuming participants who discontinue will on average contribute 5 cycles of exposure), approximately 1020 participants must be enrolled to achieve at least 7000 at-risk cycles. A minimum of 200 participants completing the study will be ensured. With 7000 at-risk cycles, the study will have 95% power for the upper limit of the two-sided 95% CI for the Pearl Index to be < 5 in the overall population, assuming that the true Pearl Index is 2 and that a Poisson model is used to achieve the CI. Myovant has powered the study based on the combined population of women with uterine fibroids or endometriosis. The study aims to enroll approximately 50% of women with uterine fibroids (with a minimum of 40%) and approximately 50% of women with endometriosis (with a minimum of 25%).

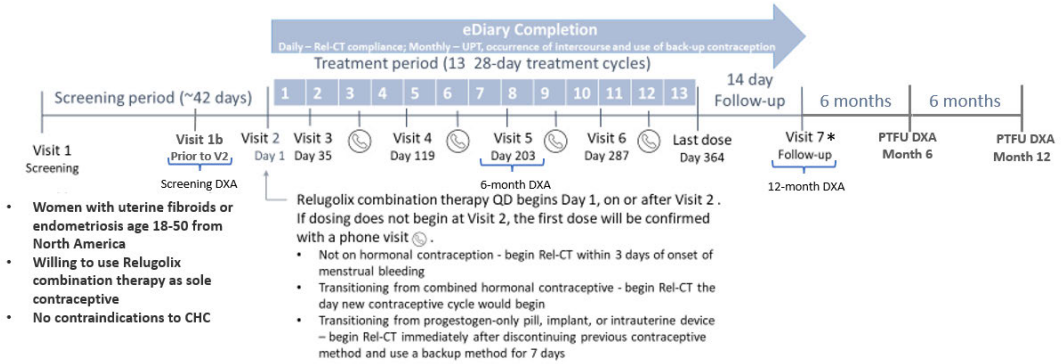
Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) 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 DSMB will be outlined in a separate charter.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: MVT-601-050 Study Schematic



Abbreviations: CHC = combined hormonal contraceptive; DXA = dual energy X-ray absorptiometry; E2 = estradiol; eDiary = electronic diary; NETA = norethindrone acetate; PTFU = post-treatment follow-up; QD = once daily; Rel-CT = relugolix combination therapy (relugolix 40 mg, E2 1 mg, NETA 0.5 mg); UPT = urine pregnancy test.
* or 14 days after the last dose.
Note: During the treatment period Visits occur approximately 7 days after the end of the previous cycle.
Phone visits occur approximately 6 weeks after the subsequent Visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities for MVT-601-050

Trial Period	**Screening**		**Allocation**	**Treatment Period**							
Visit	**V1**	**V1B**	**V2[a]**	**V3**	**P3**	**V4**	**P4**	**V5**	**P5**	**V6**	**P6**
Visit Timing	**−42 D**	**-30 D to -15 D**	**On or prior to D1[b]**	**7 days after Cycle 1**	**~6 wks after V3**	**~7 days after Cycle 4**	**~6 wks after V4**	**7 days after Cycle 7**	**~6 wks after V5**	**7 days after Cycle 10**	**~6 wks after V6**
Day of Study Intervention Treatment[c]			**D 1[d]**	**D 35**	**D 77**	**D 119**	**D 161**	**D 203**	**D 245**	**D 287**	**D 329**
Informed Consent	X										
Inclusion/Exclusion Criteria	X		X								
Medical History	X										
Gynecological History	X										
Prior and Concomitant Medication	X		X	X	X	X	X	X	X	X	X
Contraceptive History	X		X								
Columbia Suicide Severity Rating Scale[w]	X		X[x]	X[x]		X[x]		X[x]		X[x]	
Patient Health Questionnaire-9[x]			X	X		X		X		X	
Dispense eDiary			X								
eDiary Training/Re-Training[e]			X	X	X	X	X	X	X	X	X
Dispense Study Intervention			X	X		X		X		X	
eDiary Compliance/Data Review				X	X	X	X	X	X	X	X
Drug Accountability[f]				X		X		X		X	
Contraceptive Counseling										X[g]	X[g]
Physical Examination[h,i]	X										
GYN & Breast Examination[i]	X										
Height	X										
Weight, Vital Signs (HR, BP)	X		X	X		X		X		X	
Adverse Event Monitoring	X		X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests[j]	X			X		X		X		X	
Gonorrhea/Chlamydia Test	X										
Cervical Cytology[k]	X										
Mammogram[u]	X										

Serum βhCG[l]	X										
Urine Pregnancy Test[m]		X	X	X		X		X		X	
Transvaginal ultrasound[v]	X										
Bone densitometry[r]		X[s]						X		X[t]	

Table 1: Schedule of Activities for MVT-601-050 (Continued)

Trial Period	**Post-Treatment Period**				**Unscheduled**
Visit	**Follow-Up/ EOT (V7)[n]/ Early Termination**	**6-months Post-treatment[z] (PTFU 6-month)**	**12-months Post-treatment[z] (PTFU 12-month)**	**Pregnancy**	
Visit Timing	**14 days after Cycle 13 or Last Dose**	**(+/- 30 days)**	**(+/- 30 days)**	**Upon diagnosis**	
Day of Study Intervention Treatment[c]	**D378**			**NA**	**NA**
Informed Consent					
Inclusion/Exclusion Criteria					
Medical History		X[y]	X[y]		
Gynecological History					
Prior and Concomitant Medication	X	X[y]	X[y]	X	X
Contraceptive History		X[y]	X[y]		
Columbia Suicide Severity Rating Scale[w]	X[x]				X[p,x]
Patient Health Questionnaire-9[x]	X				X[p]
Dispense eDiary					
eDiary Training/Re-Training[e]					X[p]
Dispense Study Medication					X[p]
eDiary Compliance/Data Review	X			X	X[p]
Drug Accountability[f]	X			X	X[p,q]
Contraceptive Counseling	X[g]				
Physical Examination[h,i]	X			X	X[p]
GYN & Breast Examination[i]	X			X	X[p]
Height					X[p]
Weight, Vital Signs (HR, BP)	X			X	X[p]
Adverse Event Review	X			X	X
Clinical Laboratory Tests[j]	X	X	X	X	X[p]
Gonorrhea/Chlamydia Test					X[p]
Cervical Cytology[k]					X[p]
Mammogram[u]	X				
Serum βhCG[l]	X			X	X[p]

Urine Pregnancy Test[m]	X	X	X		X[p]
Transvaginal ultrasound[v]				X[o]	
Bone densitometry[r]	X[t]	X	X		

Abbreviations: βhCG = beta human chorionic gonadotropin; AGC = atypical glandular cells; AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; ALT = alanine transaminase; ASC-H = atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; AST = aspartate transaminase; BP = blood pressure; D = day(s); EDD = estimated date of delivery; eDiary = electronic diary; EOT = end-of-treatment; GGT = gamma-glutamyl transferase; GYN gynecologic; HPV = human papilloma virus; HR = heart rate; HSIL = high-grade squamous intraepithelial lesion; LDH = lactic dehydrogenase; LSIL = low-grade squamous intraepithelial lesion; NA= not applicable; P = phone contact; V = visit.

a. The timing of Visit 2 depends on the patient's contraceptive method at screening (see Table 7). Visit 2 should occur after screening test results indicating eligibility are available.
b. Study drug dosing (Day 1) occurs at or after Visit 2 and is dependent upon the patient's contraceptive method at screening. See Table 7 for instructions on initiating dosing of relugolix combination therapy.
c. Visits should be scheduled on the target day of study intervention treatment as indicated. If this this not feasible, the visit should occur as soon after the target day as possible. If a visit does not occur at the scheduled time, every effort should be made to ensure the next visit occurs on the target day indicated on the table. Treatment must not be extended beyond Day 364.
d. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact.
e. Initial eDiary training to be performed when eDiary is dispensed. eDiary training for the participant should be performed/reinforced throughout the study.
f. The participant should be asked to bring all study intervention to the clinic for each visit (see Section 6.4).
g. Counseling regarding post-trial contraceptive use should be provided to all participants at Visit 6 and repeated at Phone Visit 6 and Visit 7 (Follow-up/EOT).
h. A complete physical exam will be conducted at Visit 1 and Visit 7 and will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All other physical examinations should focus on signs and symptoms reported by the participant.
i. Physical, gynecologic, and breast examinations should be conducted by a licensed health professional (eg, physician, nurse practitioner, physician assistant).
j. Clinical laboratory tests will include hematology, chemistry with phosphate, lipid profile, thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), 25-OH vitamin D, and hemoglobin A1C at screening (see Appendix 2). The screening sample must be obtained in the fasted state (no food or drink other than water after midnight). If Visit 2 occurs > 42 days past the date of the screening laboratory assessments for any reason, all serum screening laboratory assessments should be repeated and reviewed prior to allocation of study drug. If vitamin D supplementation was started for vitamin D deficiency in the screening period, a 25-OH vitamin D level should be drawn at Visit 3. Assessments at Visits 3, 4, and 6 will otherwise only include liver function tests (ALT, AST, GGT, total bilirubin, alkaline phosphatase, lactate dehydrogenase). Visits 5 and 7 will include hematology, chemistry, serum βhCG, and lipid profile (perform TSH, PTH, 25-OH vitamin D if BMD loss > 3% or Z-score ≤ -2.0 at PTFU Month 6 or Month 12 DXA). If labs are obtained due to bone mineral density loss of > 3% or Z-score ≤ -2.0 in the post-treatment follow-up period, labs will be limited to 25-OH vitamin D, TSH, PTH, creatinine, calcium, and phosphate (see Section 8.2.4.1 for further details).
k. Cervical smear is only applicable to participants 21 years of age and older (or who will become age 21 during the course of the trial). Cervical cytology does not need to be performed if a normal cervical cancer screening result (as determined by patient age and investigator's chosen guidelines) performed within 18 months of Visit 1 can be documented and the participant does not report a history of abnormal results within the past 18 months. Cervical smear may be performed by a nurse practitioner or physician's assistant if licensed in the state, is trained, and it is within their scope of practice.
l. A serum βhCG pregnancy test is required at Visit 1 and Visit 7 (Follow-up/EOT). Serum testing should also be performed during the trial if a pregnancy is suspected, or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound).

m. A urine pregnancy test will be performed at each site visit after screening and prior to all DXA scans on the day of the DXA. If the DXA facility does not perform pregnancy tests, the site must perform a urine pregnancy test at the clinic or confirm with the patient via a phone contact on the day of the DXA that a home urine pregnancy test was completed on the day of the DXA and prior to the DXA and that the result was negative. Additionally, a home urine pregnancy test performed by the participant is required prior to the start of each cycle and the result must be negative and reported in the eDiary to continue. Any positive pregnancy test should be confirmed by a serum βhCG pregnancy test (and transvaginal ultrasound, when applicable).
n. Follow-up/EOT visit also to be done in case of early discontinuation. All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention (ie, the safety reporting period). Patients enrolling in MVT-601A-006 following completion of 13 cycles of treatment should still complete the EOT/Visit 7. Though these patients may be taking relugolix combination therapy under a different protocol, this visit should still be conducted 14 days after the last dose of treatment under MVT-601-050 (Day 378).
o. Transvaginal ultrasonography will be performed to determine gestational age/EDD.
p. For an unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
q. eDiary and any remaining drug should be collected by the site at this visit.
r. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading. A screening, 6- and 12-month on-treatment, and post-treatment follow-up (PTFU) Month 6 and Month 12 DXA will be performed within ± 30 days of the recommended time frame. For further details, see Section 8.2.6.
s. DXA should not be completed before normal baseline physical exam, pathology, laboratory studies, and pregnancy test are completed. The DXA should be performed between 30 to 15 days prior to allocation of investigational product to account for the possibility that a repeat scan will need to be performed.
t. The 12-month on-treatment DXA may occur at the end-of-treatment (EOT) visit. If performing the early termination visit, refer to Section 8.2.6.1 for detailed guidance on whether a DXA needs to be performed. For patients planning to enter MVT-601A-006 following completion of this study, the 12-month on-treatment DXA should occur as early as possible (ie, 30 days prior to last dose).
u. Patients ≥ 40 years old at the time of enrollment will need to undergo a screening mammogram if it has been ≥ 1 year past their last mammogram. They must also complete a mammogram at the EOT visit. Patients who turn 40 during the study should undergo a mammogram at the EOT visit. Patients who early terminate do not need to undergo a mammogram at the EOT visit if it has been less than one year since their screening mammogram
v. Patients with uterine fibroids for whom an ultrasound report from the last two years cannot be obtained may undergo transvaginal ultrasound at the screening visit to confirm the presence of one or more fibroids.
w. Patients must complete the Columbia Suicide Severity Rating Scale (C-SSRS) at V1 and at onsite visit if required by Section 8.2.8.
x. If review of Patient Health Questionnaire-9 (PHQ-9) shows an answer of 1+ to the question of being bothered in the last two weeks by “Thoughts that you would be better off dead, or of hurting yourself in some way,” this requires further assessment for suicidality with the C-SSRS.
y. At the time of the post-treatment follow-up DXA assessments, patients will be contacted by phone and asked to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events.
z. These PTFU assessments will be waived for participants enrolled in MVT-601A-006 following completion of treatment under this protocol. Participants who plan to enroll in MVT-601A-006 who subsequently do not meet entry criteria should still complete the PTFU assessments.

2. INTRODUCTION

Relugolix is a daily, orally active, potent, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) (relugolix combination therapy) for the treatment of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Relugolix competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are considerably reduced, with the reduction in FSH concentrations preventing natural follicular growth and development, limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Further, prevention of an LH surge inhibits ovulation, and therefore the corpus luteum does not develop, which precludes the production and secretion of progesterone into the systemic circulation. Relugolix is combined with E2 1 mg and NETA 0.5 mg to maintain E2 concentrations within a therapeutic range and progesterone/progestin concentrations at low levels, to treat symptoms associated with endometriosis and uterine fibroids while maintaining bone mineral density (BMD) and preventing vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen.

Relugolix combination therapy is intended to provide an effective and well-tolerated option for the long-term treatment of symptoms associated with endometriosis and uterine fibroids. This study will evaluate the efficacy and safety of relugolix combination therapy as a contraceptive in women with a diagnosis of uterine fibroids or endometriosis.

2.1. Study Rationale

Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Uterine fibroids and endometriosis are both prevalent conditions in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy or safety of participants undergoing treatment with relugolix combination therapy for the treatment of symptoms associated with endometriosis or uterine fibroids. This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis.

This study is being conducted in women of reproductive age with endometriosis or uterine fibroids and presumed normal fertility. By determination of the Pearl Index (PI) for relugolix combination therapy (ie, by quantifying the contraceptive effectiveness), the study will provide evidence for participants and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception during treatment with relugolix combination therapy.

2.2. Background

Replicate, randomized, double-blind, placebo-controlled, 24-week phase 3 studies followed by a long-term open-label extension study were conducted within each indication to support marketing approval. Relugolix combination therapy has been approved in the United States as MYFEMBREE® for the management of heavy menstrual bleeding associated with uterine fibroids.

To support the uterine fibroid indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with heavy menstrual bleeding associated with uterine fibroids. Patients with confirmed uterine fibroids with heavy menstrual bleeding were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (Studies MVT-601-3001 [N = 387] and MVT-601-3002 [N = 381]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open label- extension study (MVT-601-3003), designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the uterine fibroid indication.

A statistically greater proportion of women treated with relugolix combination therapy compared to placebo (73.4% vs. 18.9% [$p < 0.0001$] in MVT-601-3001 and 71.2% vs. 14.7%% [$p < 0.0001$] in MVT-601-3002) achieved the primary endpoint of both a menstrual blood loss volume of < 80 mL and at least a 50% reduction from baseline in menstrual blood loss (MBL) volume over the last 35 days of treatment. Six key secondary endpoints related to menstrual blood loss volume, amenorrhea, change in hemoglobin, pain associated with uterine fibroids as measured by a Numerical Rating Scale, and change in patient-reported distress from heavy bleeding, passing of blood clots, and pelvic pressure as assessed by the validated Bleeding and Pelvic Discomfort scale, and change in uterine volume were also met. Relugolix combination therapy-maintained BMD at levels comparable to placebo over 24 weeks and was generally well tolerated. Additionally, the long-term extension study MVT-601-3003 demonstrated durability of treatment effect for up to 52 weeks. The overall safety profile of relugolix combination therapy for up to 52 weeks was consistent with that observed over the first 24 weeks with low incidence of vasomotor symptoms and maintenance of BMD over time.

To support the endometriosis indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 1250 premenopausal women with pain associated with endometriosis. Patients with confirmed endometriosis with moderate to severe pain were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (MVT-601-3101 [N = 628] and MVT-601-3102 [N = 622]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3103) designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the endometriosis indication.

Patients receiving relugolix combination therapy achieved both co-primary endpoints by demonstrating clinically-meaningful pain reductions compared to placebo for dysmenorrhea (74.5% vs. 26.9% [$p < 0.0001$] in MVT-601-3101 and 75.2% vs. 30.4% [$p < 0.0001$] in

MVT-601-3102) and for nonmenstrual pelvic pain (58.5% vs. 39.6% [p < 0.0001] in MVT-601-3101 and 66% vs. 42.6% [p < 0.0001] in MVT-601-3102).

In study MVT-601-3101, all seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, and impact of pain on daily activities as measured by the Endometriosis Health Profile-30 (EHP-30) pain domain, greater proportions of women not using analgesics (p-values < 0.0001), changes in mean nonmenstrual pelvic pain (p = 0.0002), greater proportions of women not using opioids (p = 0.0005), and changes in mean dyspareunia (painful intercourse; p = 0.0149). In study MVT-601-3102, six of seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, impact of pain on daily activities as measured by the EHP-30 pain domain, a greater proportion of women not using opioids (all p-values < 0.0001), changes in nonmenstrual pelvic pain (p = 0.0012), and dyspareunia (painful intercourse; p = 0.0371). Relugolix combination therapy was generally well tolerated with minimal BMD loss over 24 weeks.

In addition, an ovulation inhibition study with relugolix combination therapy in healthy adult premenopausal women has been completed (MVT-601-046, N = 67). This open-label, single-arm study included a pre-treatment period to confirm ovulatory status, an 84-day treatment period to assess the effects of relugolix combination therapy on ovarian activity, and a post-treatment follow-up period to determine time to return of ovulation. Ovulation (as assessed by the Hoogland-Skouby scale [Hoogland and Skouby 1993]) was inhibited for 100% of participants during the entire 84-day treatment period, and ovarian activity, as evidenced by the degree of follicular growth, was markedly suppressed. Pituitary secretion of FSH and LH, and ovarian production of estradiol and progesterone were markedly suppressed with relugolix combination therapy, with median E2 serum concentrations consistently maintained within an approximate range of 30 to 40 pg/mL during the 84-day treatment period. Mean progesterone concentrations were consistently maintained between 0.94 and 1.25 nmol/L, with individual values all below 5 nmol/L, the cut-off value for luteal activity in the Hoogland-Skouby assessment scale, consistent with the suppression of ovulation observed across all three treatment periods. Additionally, endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness consistently maintained between 4 and 5 mm and likely contributing to the reduction in overall bleeding. All women returned to ovulation or began menses upon discontinuation of relugolix combination therapy demonstrating the revisability of the treatment effect. The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days, with 97.01% (65 of 67 participants) having a confirmed ovulation within 36 days post treatment (one participant ovulated on Day 43 and the other began menstruation on Day 39).

As of June 2021, the relugolix clinical development program includes data from 4463 participants and patients exposed to relugolix either as monotherapy or as relugolix combination therapy, and includes 2554 patients exposed for at least 6 months and 1545 patients exposed for at least one year. These data include single doses up to 360 mg and multiple doses up to 120 mg administered for more than a year. Data from the pivotal phase 3 studies in the uterine fibroid indication demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. Data from the pivotal phase 3 studies in the endometriosis indication also demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo.

These collective data continue to support a favorable benefit/risk profile for the proposed indications.

In summary, data from the relugolix nonclinical, pharmacodynamic, and clinical development program support the proposed mechanism of action for relugolix combination therapy, which works through inhibition of follicular development and prevention of ovulation, suppressing the secretion of endogenous estradiol and progesterone. Data from the completed pivotal phase 3 studies demonstrate robust efficacy results for the indications studied. Data from the ovulation inhibition study demonstrate maximal suppression of ovulation. The currently available safety database is large and allows characterization of the safety profiles of relugolix monotherapy and relugolix combination therapy to support initiation of this study. A detailed description of the chemistry, pharmacology, efficacy, and safety of relugolix is provided in the investigator brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of relugolix combination therapy may be found in the current investigator brochure.

2.3.1. Risk Assessment

On the basis of nonclinical studies, clinical safety analyses, and data available for investigations of similar compounds, relugolix combination therapy may be associated with potential risks. The risk assessment and mitigation strategies for this protocol are outlined in Table 2.

Table 2: Study MVT-601-050: Risk Assessment and Mitigation Strategies

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Identified Risk		
Uterine fibroid prolapse or expulsion.	Exclusion of participants with abnormal bleeding due to uterine fibroids or known submucosal uterine fibroids.	Active monitoring of adverse events.
Potential Risk		
Decreased Bone Mineral Density 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.	Exclusion criteria for: – History of osteoporosis, history of treatment for low BMD, current osteoporosis, or low BMD (Z-score $\leq$ -2.0 at lumbar spine, total hip, or femoral neck during the screening period), – History of or current metabolic bone disease, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, 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 BMD eligibility criteria for the study are allowed	Bone mineral density will be monitored at the Baseline, 6-Month, and 12-Month/Early Termination visits with specified discontinuation criteria. There will then be a post-treatment follow-up period with BMD measured again at 6- and 12- months after treatment (PTFU DXA Month 6 and Month 12). Active monitoring of fractures and bone health will be performed. All fractures should be reported within 24 hours of study personnel awareness.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Hepatic Transaminase Elevation Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver biochemical tests (ALT and or AST ≥ 3 x ULN) are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 × ULN; total bilirubin values > 1.5 × ULN.	Hepatic transaminases are monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009) in all relugolix studies. Abnormal liver tests (AST or ALT ≥ 3 × ULN) that develop during the treatment period will be reported within 24 hours of study personnel awareness.
Embolic and Thrombotic Events Oral contraceptives and hormone replacement therapy are associated with an increased risk for a venous or arterial thromboembolic event.	Exclusion of participants with previous or current venous thromboembolism.	Active monitoring of adverse events.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Embryofetal Toxicity In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures similar to those at the recommended human dose. No effects on embryofetal development were observed in rats in a similar study. In both rabbits and rats, no fetal malformations were present at any dose level tested that were associated with relugolix exposures similar to and approximately 733-times the exposures in women at the recommended human dose, respectively. Based on these findings, exposure to relugolix combination therapy early in the first trimester of pregnancy has the potential to increase the risk of early pregnancy loss.	Exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Tumors (Breast and Liver) Breast cancer is a hormonally sensitive tumor. There is substantial evidence that combined oral contraceptives do not increase the incidence of breast cancer. Although past studies have suggested that combined oral contraceptives might increase the incidence of breast cancer, more recent studies have not confirmed such findings. Hepatic adenomas are associated with hormonal contraceptive use and a long-term increased risk of developing hepatocellular carcinoma.	Exclusion criteria for participants with known, suspected, or a history of breast cancer or active liver disease. Exclusion of participants with BRCA mutations or other mutations associated with an increased risk of breast cancer.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase. Mammograms at screening and end-of-treatment for women who are ≥ 40 or who turn 40 during the trial. Active monitoring of adverse events.
Mood Disorders Depression has been reported with the prescribed use of GnRH receptor antagonists and agonists and with combined oral contraceptives and hormone replacement therapy.	Exclusion of participants whose mood disorder has been unstable or not well controlled. Exclusion of participants who have major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria. Exclusion of participants with history of suicidal ideation or suicidal behavior.	Screening for suicidality at baseline using a validated scale. Assessment of mood symptoms at each in-person visit using a validated scale. Active monitoring of adverse events.
Gallbladder Disease Combined hormonal therapy use may be associated with gallbladder disease.	Exclusion criteria for ALT and AST > 2 × ULN; total bilirubin values > 1.5 × ULN.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase and adverse events is performed during the treatment period.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FDA = Food and Drug Administration; GnRH = gonadotropin-releasing hormone; PTFU = post-treatment follow-up; ULN = upper limit of normal.

Adverse drug reactions associated with relugolix combination therapy in women with uterine fibroids include the nonserious adverse events of hot flush, abdominal pain, uterine bleeding, alopecia, libido decreased, irritability, hyperhidrosis, dyspepsia, and breast cyst and serious adverse events of uterine myoma prolapse and expulsion. Adverse drug reactions associated with relugolix combination therapy in women with endometriosis include the nonserious events of headache, hot flush, hyperhidrosis, back pain, arthralgia, libido decreased, metrorrhagia, and vulvovaginal dryness.

In completed phase 1, 2, and 3 studies, there were no drug-specific trends observed in mean or individual patient vital sign measurements, laboratory test results, or electrocardiogram parameters, with the exception of infrequent transient and predominantly mild hepatic transaminase elevations that were observed at a frequency comparable to that in placebo.

No new safety concerns have been identified during active ongoing monitoring.

Overall, the benefit/risk profile remains favorable for the continued development of relugolix combination therapy.

2.3.2. Benefit Assessment

Relugolix combination therapy is a once daily oral medication that has been shown to achieve 100% suppression of ovulation in an ovulation inhibition study (MVT-601-046), suggesting that with appropriate use it has the potential to be a highly effective contraceptive method. Additionally, prompt resumption of ovulation following discontinuation of relugolix combination therapy was observed, indicating the return to fertility is rapid and predictable.

The contraceptive action of relugolix combination therapy is mediated by relugolix, which suppresses follicular development and endogenous production of estrogen and progesterone. The risks of bone loss and vasomotor symptoms associated with a hypoestrogenic state, as well as endometrial hyperplasia from unopposed estrogen, are mitigated by administering relugolix in combination with E2 and NETA at low doses commonly used for hormone replacement therapy in menopause rather than the higher doses used in combined hormonal contraceptives to suppress ovulation. The low dosing of E2 and NETA in relugolix combination therapy may be considered an advantage to those who prefer to minimize the use of exogenous hormones.

Similar to continuous or extended cycle oral contraceptive regimens, relugolix combination therapy may benefit women who wish to limit cyclic bleeding for personal reasons. In the uterine fibroid studies, relugolix combination therapy was associated with an 84.3% reduction in menstrual blood loss volume and a high proportion of patients achieved amenorrhea (52.3% in MVT-601-3001 and 50.4% in MVT-601-3002). This change in the menstrual bleeding pattern may be considered as an advantage to some women.

Relugolix combination therapy has been generally well tolerated in most patients and participants, with an overall low rate of discontinuation due to adverse events.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with relugolix combination therapy are justified by the

anticipated benefits that may be afforded to participants in this study who seek effective contraception.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 3.

Table 3: Study MVT-601-050 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in women with uterine fibroids or endometriosis who are18 to 50 years of age and at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.

Objectives	Endpoints
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To evaluate change in bone mineral density during treatment with relugolix combination therapy.	• Percent change in bone mineral density from baseline to 6 and 12 months on-treatment at lumbar spine (L1-L4), total hip, and femoral neck.
• To evaluate post-treatment change in bone mineral density.	• Percent change from baseline and 12 months on-treatment (or Early Termination) to the 6-month and 12-month post-treatment time points at lumbar spine (L1-L4), total hip, and femoral neck.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

4. STUDY DESIGN

4.1. Overall Design

This is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy. Approximately 1020 sexually active women with uterine fibroids or endometriosis who are 18 to 50 years of age and will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

After participants sign the informed consent form (ICF), their eligibility will be assessed at Screening/Visit 1 (see Schedule of Activities; Table 1). A history of either uterine fibroids and heavy menstrual bleeding or endometriosis with moderate to severe pain will be confirmed.

A participant will be considered to have a history of fibroids if there is documentation of an ultrasound from the last two years showing one or more fibroids and the patient reports heavy menstrual bleeding affecting quality of life. If documentation of an ultrasound cannot be obtained, then an ultrasound may be performed locally to confirm the presence of one or more fibroids. Participants with fibroids will be asked a single question about their menstrual flow to determine eligibility (see Section 8.1.2).

Participants entering with a diagnosis of endometriosis-associated pain must have documentation of directly visualized endometriosis (either on laparoscopy or laparotomy) or histologically-

confirmed endometriosis. They will be asked two questions at enrollment to determine eligibility (see Section 8.1.2).

After a thorough review of the participant's medical history, gynecological history including contraception, and use of prior medications, their height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Screening for suicidal ideation and suicidal behavior will be performed using the Columbia Suicide Severity Rating Scale (C-SSRS). See Appendix 8 for a copy of this questionnaire. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (βhCG) to rule out pregnancy. Participants who are 40 years of age or older at the time of enrollment will need to undergo a screening mammogram locally (see Section 8.2.7) if it has been greater than or equal to one year since their last mammogram. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial), if no normal result is available from an examination within 18 months prior to screening. Screening tests for the sexually transmitted diseases (STD) gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible for rescreening once they have received adequate treatment for the identified STD (see Section 8.1.2). Participants who are noted to have vitamin D deficiency (25-OH vitamin D 12-19 ng/mL) may be supplemented with calcium and vitamin D (at a dose and frequency at the discretion of the treating clinician) to enroll. Participants who fail screening due to 25-OH vitamin D levels < 12 ng/mL may begin supplementing and subsequently be rescreened at the discretion of the treating clinician. Participants who are supplementing with vitamin D based on low screening 25-OH vitamin D level or are re-screened after vitamin D supplementation and subsequently enrolled should then have a 25-OH vitamin D level drawn at Visit 3 (see Table 1). The treating clinician can manage further supplementation based on this repeat level.

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 1b, which will consist of a BMD assessment via dual-energy X-ray absorptiometry (DXA) scan, which should be done between 30 and 15 days prior to Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies.

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. Depression screening (using the Patient Health Questionnaire-9 [PHQ-9]) will be completed. Any patient who scores a 1+ on the question of being bothered in the last two weeks by "Thoughts that you would be better off dead, or of hurting yourself in some way," will need to be further assessed for suicidality using the C-SSRS. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. Home pregnancy tests will be provided for assessment prior to each cycle as required by the study and as needed during the cycle.

If Visit 2 occurs on Days 1-3 of the menstrual cycle for participants not using any contraceptive method or using barrier contraception, or within the appropriate window for participants transitioning from another contraceptive method, the participant will begin her first treatment cycle of relugolix combination therapy by dosing with study medication at Visit 2. If the visit is not within the window to begin dosing, the participant will be dispensed the study intervention for initiation at home. When the participant reports the onset of the next menses in the eDiary or reaches the appropriate window to begin dosing if transitioning from another contraceptive method, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention. The first dose of study intervention will be confirmed by a phone visit. Once dosing of study intervention begins, the eDiary is organized by 28-day treatment cycles (ie, Cycle 1, 2, 3….), which are successive periods of 28 consecutive days. The eDiary continues with daily questions related to the intake of study intervention and the presence or absence of vaginal bleeding or spotting. At the end of each 28-day treatment cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding treatment cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding treatment cycle. Each subsequent treatment cycle starts with the result of a home pregnancy test, which must be negative and must be entered in the eDiary for a participant to continue in the study.

Participants will return to the clinic in the first week after completion of Cycle 1 for Visit 3. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Other records in the eDiary will be assessed, including use of other forms of contraception, occurrence of sexual intercourse during the first cycle (recorded once, at the end of the cycle), results of home pregnancy tests (if applicable), and the result of the protocol-required home pregnancy test prior to the start of Cycle 2. The occurrence of adverse events and use of concomitant medication since the last visit will be assessed. Body weight and vital signs will be measured. Mood and depression will be assessed using the PHQ-9. Patients who report an answer of 1+ to the question of being bothered in the last two weeks of “Thoughts that you would be better off dead, or of hurting yourself in some way” will need to be further assessed at that visit with the C-SSRS. Blood tests will be obtained. A 25-OH vitamin D level should be obtained if the treating clinician started supplementation based on vitamin D deficiency. Further supplementation following a normal repeat level will be left up to the discretion of the treating clinician. Study medication will be dispensed. Approximately 6 weeks after Visit 3, a telephone contact will be made (Phone 3; see Table 1), focusing on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable.

On-treatment site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur in the first week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Approximately 6 weeks following each on treatment site visit, the participant will be contacted by telephone (Phone 4, Phone 5, and Phone 6). The site visits will have the same assessments described for Visit 3 above. The telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as

applicable. The last on-treatment visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

On-treatment DXA scans are to be completed at 6 and 12 months (± 30 days). The 12-month on-treatment scan should be done as close to 12 months as possible but may be completed up to the time of Visit 7.

Fourteen days after completion of Cycle 13, or after early discontinuation of treatment, participants will return to the clinic for the follow-up/end-of-treatment (EOT) visit (Visit 7). All assessments done at on-treatment visits will be repeated. In addition, physical, gynecological, and breast examinations will be conducted, and blood samples will be obtained for lab tests along with serum βhCG to determine pregnancy. A mammogram will be performed, if indicated. Post-treatment contraception will be discussed and any remaining study medication and the eDiary will be collected.

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention (ie, the safety reporting period).

Any participant who has an on-treatment pregnancy or is pregnant at the follow-up/EOT visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Two post-treatment follow-up (PTFU) DXAs will be performed at 6 months and 12 months (PTFU Month 6 and PTFU Month 12), with a limited set of serum labs (25-OH vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphate) if BMD loss meets prespecified criteria of > 3% loss at any anatomic site or a participant has a Z-score of≤ -2.0. Patients will be contacted by phone at the time of these DXA assessments to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events.

Patients who enroll in MVT-601A-006 upon completion of Cycle 13 (Month12) in this study, will transition to treatment under MVT-601A-006 after completion of Cycle 13. The PTFU Month 6 and PTFU Month 12 assessments will be waived for patients who enroll in MVT-601A-006.

4.2. Scientific Rationale for Study Design

This is an open-label, single-arm, phase 3 study designed to demonstrate the contraceptive efficacy of relugolix combination therapy in the intended treatment population. The primary objective is to assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and are at risk for pregnancy, as expressed by the At-Risk PI in the restricted intent-to-treat (rITT) population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse. Study intervention will be self-administered during 13 consecutive 28-day treatment courses (“cycles”) for a total duration of 52 weeks.

To demonstrate the intrinsic contraceptive efficacy of relugolix combination therapy, a study population of women with uterine fibroids or endometriosis without known impaired fertility is considered adequate if patients have regular menstrual cycles (ie, presumed regular ovulation).

To support a proper assessment, women participating in this study should be sexually active with men and should agree to abstain from using other forms of contraception during the treatment period.

Participants will visit the study site approximately every 12 weeks for safety evaluations, which include review of adverse events, eDiary, and concomitant medications, and collection of weight, vital signs (blood pressure, heart rate), and urine pregnancy test. Clinical laboratory evaluations will occur at Visits 1, 3, 4, 5, 6 and 7. The study eligibility criteria were designed to minimize risk to participants and rules for evaluation of liver test abnormalities, consistent with FDA guidance (FDA 2009), have been incorporated into the protocol.

4.3. Justification for Dose

The relugolix combination therapy doses of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg were selected for this study as they are the proposed clinical doses in women with heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

In replicate pivotal phase 3 trials, within each of the indications studied, a 40-mg dose of relugolix combined with E2 1 mg and NETA 0.5 mg resulted in marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women and a decrease in pelvic pain associated with endometriosis, respectively. Across the development programs, the combination of relugolix with E2 and NETA at the selected doses demonstrated maintenance of BMD and prevented vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen. Across all studies, relugolix combination therapy was generally well tolerated in most participants, with an overall low rate of discontinuation due to adverse events. On the basis of the favorable benefit-risk profile observed in each indication, Myovant intends to commercialize relugolix combination therapy for the treatment of heavy menstrual bleeding associated with uterine fibroids and for pain associated with endometriosis.

In a study evaluating the effects of relugolix combination therapy on ovarian activity in healthy premenopausal women (MVT-601-046), relugolix combination therapy demonstrated inhibition of ovulation, as determined by Hoogland-Skouby score, in 100% of women receiving relugolix combination therapy during the entire 84-day treatment period. Therefore, these same doses are expected to be effective in preventing pregnancy.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed thirteen 28-day treatment cycles, the safety follow-up/ EOT visit (Visit 7), and the PTFU Month 6 and Month 12 DXAs (refer to Schedule of Activities, Table 1).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 50 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a diagnosis of uterine fibroids or endometriosis meeting *either* of the below criteria:
    a. Diagnosis of uterine fibroids by confirmation of ultrasound performed in the last 2 years (submucosal fibroids > 50% intracavitary are excluded) and patient report of heavy menstrual bleeding affecting quality of life.

       Note: If an ultrasound report from the last 2 years cannot be located, the participant should undergo transvaginal ultrasound at the time of screening to confirm the presence of one or more uterine fibroids.

    b. Diagnosis of endometriosis and has had, prior to signing the informed consent form, surgical or direct visualization (laparoscopy or laparotomy) and/or histopathologic confirmation of endometriosis, and during the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and/or during nonmenstrual portion of the cycle in the prior month;
6. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
7. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through end of treatment;
8. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
9. Has body mass index (BMI) ≥ 18 kg/m2;
10. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

5.2. Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event

(ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;

2. Has a higher risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:

    a. Vascular disease (eg, cerebrovascular disease, coronary artery disease, peripheral vascular disease);

    b. Women over 35 who smoke tobacco-containing products;

    c. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation);

    d. Inherited or acquired hypercoagulopathies, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant);

    Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;

4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;

5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);

6. Has a history of migraine with aura or focal neurological symptoms;

7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;

8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

    Note: The specific reasons for exclusion should be documented in the interactive web-response system (IWRS).

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Malabsorptive disease (including, but not limited to, inflammatory bowel disease and gastric bypass surgery);
11. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

    Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

12. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
13. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

14. Has a known history of infertility or subfertility (examples include but are not limited to prior ectopic pregnancy, prior surgery of fallopian tube, prior imaging or procedure suggesting non-patent fallopian tube, history of infertility workup or treatments);
15. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
16. Has abnormal cervical cytology or cervical biopsy in the last 18 months demonstrating:
    a. Cytology of high grade squamous intraepithelial lesion, atypical squamous cells, atypical glandular cells, or any other cytology or biopsy indicating possible or confirmed high-grade dysplasia (defined as cervical intraepithelial neoplasia [CIN] grade 2+, which includes CIN2, CIN3, adenocarcinoma in situ, and cancer) or malignancy in the genital tract
    b. Atypical squamous cells of undetermined significance or low grade squamous intraepithelial lesion cytology, unless
        - Age < 25 years, or
        - Negative for high-risk human papillomavirus (HPV), or

- Patient underwent a colposcopy after the pap smear and within 6 months of screening and there were no visible lesions *or* sampling was performed and there were no lesions showing CIN2+

c. Positive high-risk HPV test in the setting of a normal pap smear, unless:

- Age < 25 years, or
- Patient underwent a colposcopy after the pap smear and within 6 months of screening and there were no visible lesions *or* sampling was performed and there were no lesions showing CIN2+

Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial).

17. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, intermenstrual/bleeding between menstrual periods, bleeding from a cervical polyp, recurrent bleeding after intercourse);
18. Has a known submucosal fibroid (> 50% intracavitary);
19. Women with a diagnosis of endometriosis who have had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis.

Other Conditions/Disorders

20. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
21. Has known HIV infection or high risk of contracting human immunodeficiency virus (HIV) (eg, has multiple sexual partners, intravenous drug use in participant or partner);
22. Has a history of malignancy ≤ 5 years prior to signing the ICF, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
23. Has known BRCA mutation or other mutation associated with increased risk of breast cancer;
24. 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;
25. History of suicidal ideation or behavior, or confirmed "yes" to any question (with exception of non-suicidal self-injurious behavior, unless deemed as an unacceptable risk by the investigator) on the C-SSRS;
26. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair

interpretation of their data. Participants with major depression, posttraumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders (based on Diagnostic and Statistical Manual of Mental Disorders 5 [DSM-5] criteria) who have been unstable or not well controlled based on the investigator or mental health professional's judgement, 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 treatment period should not be enrolled;

27. Has a hepatic hemangioma, or has a history of cholestasis with prior estrogen use or during pregnancy;
28. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
29. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
30. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

31. Has a known or suspected pregnancy;
32. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
33. Is breastfeeding or has breastfed in the last year.

At risk of bone loss or unable to be monitored for changes in bone density

34. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
35. Has a bone mineral density Z-score $\leq$ -2.0 at lumbar spine, femoral neck, or total hip during the screening period;
36. Screening 25-OH vitamin D level < 12 ng/mL (patients with vitamin D deficiency with levels 12-19 ng/mL are permitted if supplementing with vitamin D).

    Note: If patients fail screening because of vitamin D levels, they may begin supplementing with vitamin D at the discretion of the treating clinician and be re-screened eight weeks later.

37. Has a history of or currently has osteoporosis, or other metabolic bone disease, collagen vascular disease, chronic kidney disease (CKD) stage 3 or greater with glomerular filtration rate (GFR) < 60 mL/min/m^2 using Modification of Diet in Renal Disease (MDRD) method, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, hyperthyroidism, anorexia nervosa, abnormal bone mineral metabolism (eg, hypophosphatemia), or low traumatic (fragility) fracture. 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;

38. Past history of use or current use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
39. Prior use of depo-medroxyprogesterone acetate for a treatment period > 2 years.

Concomitant and Recent Medications/Devices

40. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
41. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
42. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein);
43. Has used chronic glucocorticoids that are oral, parenteral, inhaled (prednisone equivalents of ≥ 2.5mg daily for ≥ 3 months) in 12 months prior to the study. Women with epidural or spinal glucocorticoid use at any dose in the last 12 months are excluded.

Miscellaneous

44. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

5.3. Lifestyle Considerations

No restrictions are required for treatment with relugolix combination therapy.

5.4. Screen Failures

Participants who consent to participate in the clinical study but are not subsequently entered in the study are considered to have had a screen failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any serious adverse event.

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the

study protocol. Note: the study intervention in this study is relugolix combination therapy, also referred to as either relugolix combination therapy, study medication, or study drug.

6.1. Study Intervention(s) Administered

Fixed-dose combination (FDC) tablets, each consisting of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg will be supplied as immediate-release, yellow, film-coated tablets. In addition to the three active pharmaceutical ingredients, the core tablet formulation consists of compendial grade excipients including mannitol, lactose monohydrate, sodium starch glycolate, hydroxypropyl cellulose, and magnesium stearate.

The study intervention is presented in Table 4.

Table 4: Study MVT-601-050 Study Intervention

Intervention Name	**Relugolix Combination Therapy**
Type	Drug
Dose Formulation	Round film-coated yellow tablet
Unit Dose Strength	FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg)
Dosage Level(s)	Single FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg) QD
Route of Administration	Oral
Use	Experimental
IMP/NIMP	IMP
Sourcing	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee
Packaging and Labeling	Study intervention will be provided in a bottle or blister package. Each will be labeled as required per US requirements.

Abbreviations: E2 = estradiol; FDC= fixed-dose combination; IMP = investigational medicinal product; NETA = norethindrone acetate; NIMP = non-investigational medicinal product; QD = once daily; US = United States.

6.2. Preparation/Handling/Storage/Accountability

Relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablets are supplied to the study site in a bottle or blister cards with 28 tablets. The FDC tablets should be stored in the original closed bottle or blister card.

All study participants will take study intervention comprising one tablet daily at approximately the same time.

If a dose is missed, instructions are as follows:

- If a dose is missed and the error is recognized on the same calendar day, the study intervention should be taken as soon as possible, and then regular dosing should be resumed the next calendar day at the usual time.

- If the missed dose is not recognized until the next calendar day (one missed dose), the dose intended for that calendar day should be taken as soon as possible, and regular dosing should be resumed the following day at the usual time.
- If 2 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time.
- If 3 to 6 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time. Back-up contraception should be used for 7 days. Emergency contraception may be administered per current practice if the patient has unprotected intercourse during the missed pill interval and should be noted in the concomitant medications section. The medical monitor should be contacted.
- If 7 or more consecutive days are missed, the participant should begin using back-up contraception immediately and should be seen for an unscheduled visit. Emergency contraception may be administered per current practice if the patient has unprotected intercourse during the missed pill interval and should be noted in the concomitant medications section. The medical monitor should be contacted.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. Although participants and investigators are not blinded to the study treatment or the study outcome (pregnancy), bias is limited because the diagnosis of pregnancy is an objective measure.

6.4. Study Intervention Compliance

Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles"), for a total duration of 52 weeks (364 days). Participants should complete their eDiary each day on study and should bring all remaining study intervention and all used study intervention packages to each study visit. Compliance with daily intake of study intervention

will be assessed based on drug accountability and records in the eDiary. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for dose interruptions will also be recorded in the eCRF.

6.5. Concomitant Therapy

Concomitant or prior therapies must be recorded including:

- Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements) from signing the ICF through the end of the study; or
- Any vaccine, immunization, or hormonal contraceptive method from 6 months prior to signing the ICF through the end of the study;

This information must be recorded in the following ways:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Medications

Table 5 provides examples of prohibited drug categories, as well as details about required washout intervals prior to screening; however, it is not a comprehensive list of all restricted medications. Patients currently taking prohibited medications or medications that require washout intervals should not discontinue these medications solely to participate in this study. In the event that patients require treatment with any of these medications during the post-treatment follow-up period, treatment should not be withheld. Consult the medical monitor if there is any uncertainty regarding participant use of a particular drug or drug class.

Table 5: Study MVT-601-050 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class and Effect	Examples	Comments
	Prohibited Medications	
Bisphosphonates	alendronate etidronate zoledronic acid risedronate ibandronate clodronate tiludronate	Any past use is exclusionary per exclusion criterion 38.

Drug Class and Effect	Examples	Comments
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Any past use is exclusionary per exclusion criterion 38. Calcium and vitamin D2 and vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	Washout interval prior to initiation of relugolix combination therapy: 3 months Note: All other anticonvulsants are allowed.
Oral P-glycoprotein (P-gp) inhibitors*	**Antianginal medications**: ranolazine **Antiarrhythmic medications**: amiodarone, dronedarone, propafenone, quinidine **Antifungals**: ketoconazole, itraconazole **Antihypertensives**: carvedilol, verapamil **Anti-infectives**: azithromycin, clarithromycin, erythromycin, tetracycline **Hepatitis C medications**: glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir **HIV medications**: cobicistat, cobicistat-containing combinations, ritonavir, ritonavir-containing combinations (eg, lopinavir/ritonavir), indinavir **Immunosuppressants**: cyclosporine **Kinase inhibitors**: lapatinib, vemurafenib	Washout interval prior to initiation of relugolix combination therapy is 5 half-lives or 14 days, whichever is longer. Washout interval for amiodarone is 6 months. If a limited course of an oral P-gp inhibitor is required during the study, see Table 6.
Combined p-glycoprotein and strong CYP3A inducers	carbamazepine lumacaftor (available only in combination with ivacaftor as Orkambi®) mitotane phenobarbital phenytoin rifampin rifapentine St. John's wort	Washout interval of 28 days prior to initiation of relugolix combination therapy, with exception of carbamazepine and phenobarbital, for which the washout period is 3 months.

Drug Class and Effect	Examples	Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	Exclusionary if patient has anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of greater than or equal to 2.5 mg every day during the study. Note: Spinal or epidural glucocorticoids are prohibited at any dose. Topical, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Washout interval prior to initiation of relugolix combination therapy: 12 months If a limited course of glucocorticoids is required during the study, see Table 6.
GnRH antagonists/agonists	leuprolide acetate injection, such as leuprorelin or goserelin acetate injections elagolix	Washout interval prior to initiation of relugolix combination therapy: 3 months (6 months for 3-month injections)
Anti-androgens	danazol	Washout interval prior to initiation of relugolix combination therapy: 4 months
Aromatase inhibitors	anastrozole letrozole	Washout interval prior to initiation of relugolix combination therapy: 4 months
Selective estrogen receptor modulators	raloxifene bazedoxifene asofoxifene clomifene tamoxifen	Washout interval prior to initiation of relugolix combination therapy: 2 months
Selective progesterone receptor modulators	mifepristone ulipristal acetate	If used as a daily medication, washout interval prior to initiation of relugolix combination therapy: 6 months If used in the 6 months prior to enrollment as a single dose for emergency contraception or medication abortion, there is no washout interval, provided the patient has completed follow-up and absence of pregnancy is confirmed.

Drug Class and Effect	Examples	Comments
Proton pump inhibitor	Omeprazole esomeprazole pantoprazole rabeprazole dexlansoprazole lansoprazole	Washout interval prior to initiation of relugolix combination therapy: 3 months
Anti-coagulants/ platelets/fibrinolytics	Warfarin heparin low molecular weight heparin clopidogrel tranexamic acid vitamin K preparations Factor Xa inhibitors	Washout interval prior to initiation of relugolix combination therapy: 3 months
SGLT-2 inhibitors	Ertugliflozin dapagliflozin empagliflozin canagliflozin	Washout interval prior to initiation of relugolix combination therapy: 3 months
Thiazolidinediones	Rosiglitazone pioglitazone	Washout interval prior to initiation of relugolix combination therapy: 3 months
Hormones and Contraceptives Prohibited During Treatment with Relugolix Combination Therapy		
Hormonal contraceptive pills, patches, and vaginal rings	combined or progestin-only Nuva Ring®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3.
Progestins	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel drospirenone	Washout interval prior to initiation of relugolix combination therapy: 2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	Washout interval prior to initiation or relugolix combination therapy: 2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Long-acting injectable hormonal contraceptives	depot medroxyprogesterone acetate	Prior use > 2 years is exclusionary. If use is < 2 years, washout period prior to initiation of relugolix combination therapy is 24 months.
Progestin implants and intrauterine devices	Nexplanon® Mirena® Paragard®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3.

Abbreviation: GnRH = gonadotropin-releasing hormone.
* The list of P-gp inhibitors is not comprehensive.

6.5.2. Management of Concomitant Medications, Study Drug, or Background Medications to Mitigate a Clinically Meaningful Drug Interaction

Recommendations for managing concomitant medications and study drug to mitigate a clinically meaningful drug interaction are provided in Table 6. This information is intended to provide guidance when a clinical situation arises in which a patient requires a limited course of the specific types of medications listed below during the treatment period. Please discuss management of concomitant medications with the medical monitor prior to administration.

Table 6: Management of Concomitant Medications

Drug Class and Effect	Examples	Comments
Oral P-glycoprotein (P-gp) Inhibitors*	**Antianginal medications**: ranolazine **Antiarrhythmic medications**: amiodarone, dronedarone, propafenone, quinidine **Antifungals**: ketoconazole, itraconazole **Antihypertensives**: carvedilol, verapamil **Anti-infectives**: clarithromycin, erythromycin, tetracycline **Hepatitis C medications**: glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir **HIV medications**: cobicistat, cobicistat-containing combinations, ritonavir, ritonavir-containing combinations (eg, lopinavir/ritonavir), indinavir **Immunosuppressants**: cyclosporine **Kinase inhibitors**: lapatinib, vemurafenib	If a limited course of an oral P-gp inhibitor cannot be avoided during the study, contact the medical monitor for further discussion and instructions.
Glucocorticoids	prednisolone or prednisone dexamethasone	Topical, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) glucocorticoids required for acute events are permitted during the study. For patients who require longer treatment courses (21+ days) or spinal or epidural glucocorticoids, the medical monitor should be contacted.

* The list of P-gp inhibitors is not comprehensive

6.6. Dose Modification

The dose level of relugolix combination therapy cannot be modified because it is administered as a single daily tablet.

Participants 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. Back-up contraception should be advised, as appropriate. Participants may subsequently be re-started on study intervention with the written approval of the sponsor (or designee).

6.7. Intervention After the End of the Study

Not applicable to study MVT-601-050.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Any adverse event that is intolerable to the participant 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 participant if dosing continued;
- If it is discovered after enrollment that a participant failed to meet protocol entry criteria and continued participation would pose an unacceptable risk to their health;
- If the following liver test abnormalities develop, study intervention should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until their laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 × ULN; or
  - ALT or AST > 5 × ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QTc corrected using Fridericia's formula (QTcF) prolongation of more than 500 msec on an electrocardiogram done as part of patient care outside of the study protocol;
- If the patient experiences a fragility fracture, develops a Z-score ≤ -2.0, or experiences > 3% loss of BMD at lumbar spine, total hip, or femoral neck compared with the baseline measurement during study participation. In the event of a DXA demonstrating Z-score ≤ -2.0 or BMD loss >3 %, a second DXA scan will be conducted within 30 days and the two DXA results will be averaged. If the average after repeat confirms this level of bone loss, these patients will need to discontinue the study medication and should remain in the trial for PTFU DXA assessments (see Section 8.2.6);

- Participants who are, in the opinion of the investigator or medical monitor, grossly noncompliant with the protocol requirements. Gross noncompliance includes < 75% compliance with the study intervention over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive visits) with < 50% of the required number of eDiary entries. Investigators will follow-up with the participant to encourage compliance with study intervention or eDiary prior to discontinuing her from the study;
- If the participant becomes pregnant at any time after signing the ICF, she must be withdrawn immediately (see Section 8.3.5 for information on pregnancy reporting);
- Suicidal thoughts or behavior, as confirmed on the C-SSRS (see Section 8.2.8).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. The medical monitor should be consulted in advance of withdrawal whenever possible.

At the time of discontinuing from the study, an EOT visit should be conducted, if possible. See the Schedule of Activities (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed, including post-treatment DXA scans and serum labs.

The participant will be permanently discontinued from the study intervention at that time.

The participant retains the ability to remain in the study for post-treatment bone density follow-up as per protocol.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known

mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1). Guidelines to address study conduct related to restrictions arising from the novel coronavirus 2019 global pandemic are addressed in Appendix 9.

8.1. Efficacy Assessments

8.1.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time point as described in the Schedule of Activities (see Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1.2. Screening Period

The screening period is defined as the time between the screening visit and Visit 2. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, cervical cancer screening) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (see Table 1).

Prior to conducting any screening procedures, participants will be given a full description of the nature and purpose of the study and will be required to provide written informed consent. The investigator or a designated, medically qualified member of the site staff will interview potential participants and establish their eligibility for inclusion. Potential participants will be screened according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively).

The participant's medical history, gynecological history including contraception, and use of prior medications will be reviewed. Menstrual history will be assessed to ensure the participant has a history of regular menstrual cycles every 21 to 35 days when not using hormonal contraception. If the menstrual cycle duration observed during the screening period does not meet eligibility criteria, screening may be extended with approval of the medical monitor.

A history of either uterine fibroids and heavy menstrual bleeding or endometriosis with moderate to severe pain will be confirmed.

A participant will be considered to have a history of fibroids if there is documentation of an ultrasound from the last two years showing one or more fibroids and the patient reports heavy menstrual bleeding affecting quality of life. If documentation of an ultrasound cannot be obtained, then an ultrasound may be performed locally to confirm the presence of one or more fibroids.

At the screening visit, prior to medical review, participants with fibroids will be asked a question about their menstrual flow to determine eligibility. Participants will be allowed to enroll if they answer "yes."

1. **Uterine Fibroid Menstrual Bleeding Severity [UFMBS] (screening)**:Do you have heavy blood flow during your period that makes your quality of life worse?

   No
   Yes

Participants with a diagnosis of endometriosis-associated pain must have documentation of directly visualized endometriosis (either on laparoscopy or laparotomy) or histologically confirmed endometriosis. They will be asked two questions at enrollment to determine eligibility:

Endometriosis-Associated Pain Severity [EAPS] (screening)
Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button.

1. How would you rate your worst pelvic pain on days you were having your most recent period (meaning, being on your period)?

   Absent
   Mild
   Moderate
   Severe
   Very Severe

2. During the last month, how would you rate your worst pelvic pain on days you were **not** having your period (meaning, **not** on your period)?

   Absent
   Mild
   Moderate
   Severe
   Very Severe

Participants with confirmed endometriosis who answer moderate, severe, or very severe to either question are eligible to participate.

The participant's height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including thyroid-stimulating hormone (TSH),

parathyroid hormone (PTH), 25-OH vitamin D, and βhCG to rule out pregnancy. A mammogram will be obtained, if indicated. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening tests for the STDs gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible to continue screening once they have received adequate treatment for the identified sexually transmitted disease and if the investigator determines the participant is not at high risk for reinfection (eg, because of multiple sex partners or an untreated partner). Screening for suicidal ideation and behavior will be completed using the C-SSRS. A baseline bone density assessment will be performed via DXA scan 15-30 days prior to the planned Visit 2. If Visit 2 occurs greater than 42 days past the date of the screening laboratory assessments for any reason, all serum screening laboratory assessments should be repeated and reviewed prior to allocation of study drug. In the event that the screening period is extended, every effort should be made to have the patient undergo DXA scan as close to 15-30 days prior to Visit 2 as possible.

8.1.2.1. Rescreening

Participants who fail screening may be rescreened with approval of the medical monitor. Participants who are screen-failed based on 25-OH vitamin D level < 12ng/mL may be supplemented with vitamin D and calcium at the discretion of the treating clinician and then be re-screened after eight weeks. The option to continue supplementation during the study is left to the discretion of the treating clinician. In addition, patients who were previously screen failed under Amendment 2 and 3 for an abnormal pap smear or positive high-risk HPV test who no longer meet current exclusion criterion #16 may be rescreened with permission of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

8.1.2.2. 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. Other procedures, including cervical cytology, can be retested once without the permission of the medical monitor if necessary due to technical or logistical issues, such as an inadequate sample. Further retesting or retesting for other reasons requires the approval of the medical monitor.

8.1.3. Treatment Allocation

Participants who meet all eligibility criteria, including history, laboratory test, mammogram if indicated, cervical cytology results, negative screening for suicidal ideation and behavior, and a normal bone density as determined by DXA scan will return for Visit 2, the timing of which depends on contraceptive status at screening. All use of contraceptives must be discontinued prior to Visit 2 (or on the day of Visit 2 if transitioning from an intrauterine device or contraceptive implant).

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be

captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an eDiary, which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. The first dose of study intervention will be administered on site at the time of Visit 2 or at home as described below. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact. Home pregnancy tests will be provided for assessment prior to each 28-day treatment cycle as required by the study and as needed during the cycle.

8.1.3.1. Timing of Visit 2 and Initiating Relugolix Combination Therapy

Table 2 contains instructions for scheduling Visit 2 (the allocation visit) and initiating relugolix combination therapy based on the patient's current contraceptive method.

Table 7: Timing of Visit 2 and Treatment Allocation

Previous Contraceptive Method/Hormone Preparation	Timing of Visit 2	Timing of Relugolix Combination Therapy First Dose
None/Barrier Method	Schedule in the 7 days prior to anticipated menses or Days 1-3 of menses	Days 1-3 of menses (as close to Day 1 as possible)
Combined Hormonal Contraceptives containing both Estrogens and Progestins	Schedule the allocation visit in the 7 days prior to the day a new contraceptive cycle would begin, or the day a new contraceptive cycle is scheduled to begin. Note: if a patient is using continuous combined hormonal contraceptives (ie, no pill-free, patch-free, or ring-free interval), schedule the allocation visit at any time during the month; the last pill or last day of patch/ring should be the day prior to Visit 2.	The day a new contraceptive cycle would begin. If Visit 2 falls on the day a new contraceptive cycle is set to begin, then relugolix combination therapy should be started at the allocation visit. If Visit 2 occurs in the 7 days prior to this date, then relugolix combination therapy should be started at home on the day a patient would normally start a new pill pack, patch, or ring. Patients who use combined hormonal contraceptives continuously (ie, do not have a pill-free interval, patch-free interval, or ring-free interval) can start relugolix combination therapy the day after the last active pill, or the day after the patch or ring is removed.

Previous Contraceptive Method/Hormone Preparation	Timing of Visit 2	Timing of Relugolix Combination Therapy First Dose
Oral progestin-only contraceptives (norethindrone 0.35 mg, drospirenone 4 mg)	Norethindrone 0.35mg: Schedule the allocation visit at any time during the pill pack; last dose of norethindrone should be the day prior to the allocation visit Drospirenone 4 mg: Schedule the allocation visit in the 7 days prior to the day a new contraceptive cycle would begin or the day a new contraceptive cycle is set to begin.	For patients using norethindrone 0.35 mg: in-clinic at Visit 2 (the day after the last dose of norethindrone) For patients using drospirenone 4 mg: the day a new contraceptive cycle would begin. If Visit 2 falls on the day a new contraceptive cycle is set to begin, then relugolix combination therapy should be started at the allocation visit. If Visit 2 occurs in the 7 days prior to this date, then relugolix combination therapy should be started at home on the day a patient would normally start a new pack. **A backup method must be used for 7 days.**
Levonorgestrel Intrauterine Device/Etonogestrel Implant/Copper Intrauterine Device	Schedule the day of removal of the implant or intrauterine device.	The day of removal of the device. **A backup method must be used for 7 days.** Note: if patient is transitioning from a copper intrauterine device, effort should be made to remove the device and start relugolix combination therapy on days 1-3 of menses. In this case, a backup method is not required.

8.1.4. Treatment Period

Once dosing of study intervention has been initiated, participants will take their study intervention QD. Dosing of study intervention will be organized by "cycles" of successive periods of 28 days. Participants will self-administer study intervention through the completion of Cycle 13. Participants will record compliance with study intervention dosing daily in their eDiary. They will also report information about vaginal bleeding or spotting on a daily basis. At the end of each cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has

occurred during the preceding cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding cycle. Each subsequent cycle starts with the result of a home pregnancy test, which must be negative and entered in the eDiary for the participant to continue the study.

8.1.4.1. Site Visits

Participants will return to the clinic the first week after completion of Cycle 1 for Visit 3.

Subsequent site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur 1 week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Study medication will be dispensed at each visit. See the Schedule of Activities (see Table 1) for assessments required for each visit.

8.1.4.2. Telephone Visits

Approximately 6 weeks following each site visit, the participant will be contacted by telephone (Phone 3, Phone 4, Phone 5, and Phone 6). The first telephone contact will occur approximately 6 weeks after Visit 3. Telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last on-treatment telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed. Telephone visits in the post-treatment follow-up period are outlined in Section 8.1.5.5.

8.1.4.3. 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 participant'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 (hematology and chemistry), urine or serum pregnancy testing, study intervention compliance, and dispensation of study intervention may be conducted as needed. If the unscheduled visit is related to mood changes, conduct depression and suicidality assessments using the PHQ-9 and C-SSRS as appropriate. Consult with the medical monitor, if needed, to discuss unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled DXA.

8.1.5. Post-Treatment Period

8.1.5.1. End-of-Treatment Visit

Two weeks after completion of Cycle 13, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on treatment visits will be repeated, and final status assessed; in addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for all labs, as well as serum βhCG to determine pregnancy. A mammogram will be completed, if indicated. A DXA scan will be obtained. Post-treatment

follow-up of bone density will be discussed, including time points for post-treatment follow-up DXA at Month 6 and Month 12, and serum labs, if patient meets pre-specified criteria. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

8.1.5.2. Adjustment of Procedures and Processes Associated with the End-of-Treatment Visit for Patients Enrolling in MVT-601A-006

Upon completion of 13 cycles of treatment under this protocol, patients will have the option of entering into MVT-601A-006 for an additional three years of treatment.

Patients choosing to enroll in this additional study will complete the screening visit and procedures for MVT-601A-006 during the last 6 weeks of MVT-601-050 and should undergo the 12-month on-treatment DXA as early as possible (ie, 30 days prior to the end of treatment) to ensure DXA results are available for confirmation of eligibility for MVT-601A-006. It is critical that eligibility be confirmed as early as possible to ensure study drug from MVT-601A-006 will be available to start following completion of treatment under MVT-601-050.

If patients have opted to enroll in MVT-601A-006, they will still undergo all assessments at the follow-up/EOT visit (Visit 7) 14 days after the last dose under MVT-601-050, in order to ensure that all on-treatment pregnancies are noted, as well as fulfill requirements related to the 12-month visit in MVT-601-006. For these patients, relugolix combination therapy must be noted as a concomitant medication at Visit 7.

8.1.5.3. Early Termination Visit

If the participant does not complete the study for any reason (including investigator discretion), the reason and circumstances for the participant's early termination must be fully documented. If possible, the assessments specified for the follow-up/EOT visit (Visit 7) should be performed 14 days after the last dose of study drug. If early termination occurs at an unscheduled visit or at a visit other than Visit 7, every effort should be made to have the patient return for the follow-up/EOT visit (Visit 7) fourteen days after the last dose. If early termination occurs outside of an in-person visit and the circumstances for early termination do not require an unscheduled visit or pregnancy visit, then the patient should return 14 days after the last dose for the follow-up/EOT visit (Visit 7). Patients may complete some of the follow-up/EOT visit assessments at the unscheduled visit at which early termination is decided (eg, a physical exam, breast exam, etc.), but they must complete all assessments by the time of the EOT visit and a serum pregnancy test must be completed at the follow-up/EOT visit 14 days after the last dose of study drug.

See Section 8.2.6 for instructions regarding DXA scans associated with early termination. The medical monitor should be consulted in advance of withdrawal whenever possible. Participants who are withdrawn from the study may not be re-enrolled.

A mammogram does not need to be performed at the time of early termination if it has been less than one year since the patient's last screening mammogram.

8.1.5.4. Pregnancy Visit

If a participant has an on-treatment pregnancy, the site must discontinue the participant from study intervention immediately and have her return for a visit (see Table 1). In addition to the

procedures noted in Table 1 (with exception of metabolic bone associated laboratory assessments and DXA) the participant will undergo the following diagnostic procedures:

- Quantitative serum pregnancy test (unless pregnancy already confirmed by transvaginal ultrasound);
- Transvaginal ultrasonography to determine gestational age/estimated date of delivery (EDD).

8.1.5.5. Post-Treatment Follow-Up Month 6 (PTFU Month 6) and Post-Treatment Follow-up Month 12 (PTFU Month 12)

Patients will be contacted at the time of the PTFU Month 6 and PTFU Month 12 DXA assessments via two telephone visits (PTFU Month 6 and PTFU Month 12) to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events.

If DXA scans at 6- or 12-months post-treatment show BMD loss > 3% from pre-treatment baseline or a Z-score of ≤ −2.0 at any measured anatomic site, patients are to undergo a set of metabolic bone laboratory assessments (see Section 8.2.4.1) and should be referred to a bone specialist and a deidentified copy of the specialist's evaluation should be sent to the sponsor.

If participants enroll in MVT-601A-006 upon completion of Cycle 13 (Month12), the PTFU assessments at 6 months and 12 months performed under this MVT-601-050 protocol will be waived. If a patient enrolls in MVT-601A-006 and subsequently does not meet inclusion criteria, she should remain in MVT-601-050 for PTFU DXAs.

8.1.6. Efficacy Evaluations

Planned time points for efficacy assessments are provided in the Schedule of Activities (see Table 1).

8.1.6.1. Pregnancy Testing

The contraceptive efficacy of relugolix combination therapy will be evaluated using the number of on-treatment pregnancies. On-treatment pregnancies are pregnancies with an estimated conception date (ECD) between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Pregnancy testing is conducted per the Schedule of Activities (see Table 1) as follows:

- A serum βhCG pregnancy test is performed at Visit 1 and Visit 7. Serum testing is also performed during the treatment period if an on-treatment pregnancy is suspected or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound). A urine pregnancy test is performed at all site visits after screening and as needed;
- A home urine pregnancy test performed by the participant is required prior to the start of each cycle, and the result must be negative to continue on study. Any on-treatment positive pregnancy test should be confirmed by a serum βhCG pregnancy test (and transvaginal ultrasound when applicable).

- A pregnancy test must be performed prior to each DXA scan on the day of the DXA. If the DXA facility does not perform pregnancy tests, the patient may come to the site for a pregnancy test or take a pregnancy test at home. The clinic must confirm negative result on the day of the scan and prior to the DXA scan.

8.1.6.2. Participant eDiary

All participants enrolled in the study will be provided a device with an application for a participant eDiary at Visit 2, along with detailed instructions for its use. Participants will complete daily eDiary entries including compliance with study intervention dosing and occurrence of vaginal bleeding and its severity (spotting, light, moderate, heavy, and extremely heavy), and monthly assessments of occurrence of sexual intercourse, use of back-up contraception, and home urine pregnancy test results. The eDiary data will be reviewed by the study staff on an ongoing basis and at specified time points as noted in the Schedule of Activities (see Table 1).

8.2. Safety Assessments

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), DXA, mammogram, and clinical laboratory tests. Planned time points for all safety assessments are provided in the Schedule of Activities (see Table 1).

8.2.1. Physical Examinations

A complete physical examination, including gynecological and breast examination, will be conducted at Visit 1 and the follow-up/EOT visit (Visit 7). The examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. Height and weight will also be measured and recorded.

All other physical examinations should focus on signs and symptoms reported by the participant to assess for clinically significant changes from the baseline assessment.

The gynecologic examinations at screening will include testing for gonorrhea and chlamydia. Cervical cytology test must be conducted for participants 21 years or older (or who will become 21 years old during the trial) without an available test result from within 18 months prior to the Screening Visit and submitted to the central laboratory. A repeat test should be performed for inadequate specimen and submitted to the central laboratory.

A bilateral breast examination will be performed at the time of the gynecologic examination.

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

8.2.2. Vital Signs

Vital signs including heart rate and systolic and diastolic blood pressure will be assessed. Vital signs will be measured with the participant in a seated position and should be preceded by at least 5 minutes of rest with the participant in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

Electrocardiograms are not routinely collected during the study and are to be performed per general clinical safety assessment, as applicable.

8.2.4. Clinical Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Table 1) for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within two weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Table 1).

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, serious adverse event, adverse event, or discontinuation of study intervention), then the results must be recorded in the eCRF**.**

8.2.4.1. Conditional Clinical Laboratory Tests for Prespecified Bone Mineral Density Loss

Participants who have a decline in BMD of > 3% or a Z-score ≤ -2.0 at any anatomic site (lumbar spine, total hip, or femoral neck) compared with pre-treatment baseline are required to undergo a metabolic bone laboratory assessments (25-OH vitamin D, TSH, PTH, creatinine, calcium, and phosphate). If this BMD loss occurs at the on-treatment 6-month or 12-month time point, then 25-OH vitamin D, TSH, and PTH should be drawn in addition to the standard set of safety labs at Visit 5 and Visit 7 (which include calcium, creatinine, and phosphate). If this BMD loss occurs in a different setting than the 6-month or 12-month DXA (eg, for early termination, PTFU Month 6, or PTFU Month 12), the patient must have 25-OH vitamin D, TSH, PTH, creatinine, calcium, and phosphate drawn as there are no safety laboratory assessments of this type that are pre-specified per protocol at those time points. Conditional laboratory tests should only be drawn in the setting of confirmed bone mineral density loss.

8.2.5. Ultrasound Examinations

Ultrasound examinations are not routinely scheduled throughout this study. In the event that a participant reports a history of fibroids and heavy menstrual bleeding but no documentation of fibroids from the last two years can be obtained, the participant should undergo a transvaginal ultrasound locally to confirm the presence of one or more fibroids.

Ultrasounds will otherwise occur only on an as-needed basis during the study.

8.2.6. 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) at the time points described in the Schedule of Activities (see Table 1). The scans will be read by the central imaging 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 be used at each site and operated in the same scan mode for all scans for an individual patient.

The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study. The following procedures will be followed, per the central imaging laboratory's charter: If all four vertebral levels are not visualized or if a given image set is of insufficient quality to allow proper interpretation, a query will be issued to the investigator to check whether a repeat scan can be performed. If required anatomy is missing from an image and a repeat scan cannot be obtained, it will not be analyzed. Bone density analysis of DXA scans will only be performed when at least 2 evaluable vertebrae are present. In the event that follow-up data are technically inadequate, not compliant with acquisition parameters, unreadable, unable to be re-captured in a timely manner, or electronically/physically missing, the central radiology site will enter "not assessable" into the database.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the baseline, 6- and 12-month on-treatment time points, as well as at 6- and 12-months post-treatment. At the time of these DXA assessments, patients will be asked to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events. A limited set of serum labs will be performed if bone mineral density monitoring at any time point demonstrates loss of > 3% compared to pre-treatment baseline or a Z-score of ≤ -2.0. Note that a pregnancy test will need to be completed prior to each DXA.

Participants who develop BMD decline (compared to pre-treatment baseline) of > 3% or a Z-score ≤ -2.0 at any anatomic site (lumbar spine, total hip, or femoral neck) will undergo repeat DXA scan to confirm this measurement within 30 days of the first DXA scan. The two DXA results will be averaged. If the average after repeat confirms this level of bone loss, follow-up of DXA findings will proceed according to the following rules:

- Patients who are on-treatment must be discontinued from study medication and should remain enrolled in the study for post-treatment follow-up bone mineral density monitoring (see Section 7.1). In addition, they should have a limited set of metabolic bone laboratory assessments completed (see Section 1.3) and should be referred to a bone specialist.
- Patients who are in the post-treatment follow-up period should have a limited set of metabolic bone laboratory assessments completed. In addition, they will need to be referred to a bone specialist.

If a patient meets criteria for referral to a bone specialist, the sponsor will provide a report that outlines the background of the study as well as the patient's laboratory and DXA results during

the study. This information should be sent to the bone specialist along with the patient referral. The site should send a de-identified summary of the evaluation and management plan to the sponsor once available.

8.2.6.1. Bone Mineral Density Monitoring in the Setting of Early Termination

In the event of early termination due to reasons unrelated to bone density loss, DXA scans should be obtained according to the following rules:

For early termination occurring **prior to completing 6 cycles of study medication**, an early-termination DXA scan is not required. The participant can proceed with PTFU DXA Month 6 and Month 12, along with serum labs if prespecified criteria for bone loss are met.

- For early termination occurring **after completing 6 cycles of study medication**, the patient should complete a DXA at the time of early termination and then PTFU DXA Month 6 and Month 12 and serum labs if prespecified criteria for bone loss are met.

If the 6-month on-treatment DXA was completed within the last 6 weeks and the patient has completed fewer than 8 cycles of study medication, an early termination DXA does not need to be performed and the patient can proceed to PTFU DXA Month 6 and Month 12, along with serum labs, if indicated.

8.2.6.2. Bone Mineral Density Monitoring for Patients Enrolling in MVT-601A-006

The PTFU Month 6 and PTFU Month 12 DXA assessments will be waived for patients who enroll in MVT-601A-006 following completion of 13 cycles of treatment under this protocol. For patients who choose to enroll in MVT-601A-006, the 12-month on-treatment DXA should be completed as early as possible (ie, 30 days prior to Month 12). If a patient does not meet inclusion criteria for MVT-601A-006 following the 12-month on-treatment DXA scan in this study, then the patient should remain in MVT-601-050 for PTFU assessments.

8.2.7. Mammogram

Participants who are ≥ 40 years of age at the time of enrollment will need to undergo a screening mammogram (this requirement is waived if it has been less than one year since their last mammogram and the report is obtained) and again at the end of treatment visit. If a patient turns 40 years old during the trial, she should have a mammogram completed at the end-of-treatment visit.

All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 7) and recorded in the eCRF. The following actions will be taken depending on the reading:

- Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;
- Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;
- Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours;

- Patients who have malignant breast lesion(s) or breast carcinoma will not be eligible to participate, per exclusion criteria. If at the end of the study, these patients should be referred to a breast oncologist as soon as possible.

8.2.8. Suicidal Ideation, Depression, and Behavioral Risk Monitoring

All patients will be screened for suicidal ideation and behavior at the screening visit using the C-SSRS. Patients with a confirmed answer of "yes" to any question (with exception of non-suicidal self-injurious behavior) will not be eligible to participate, as per the exclusion criteria. Patients who report non-suicidal self-injurious behavior should not be enrolled if the investigator considers participating in the trial to pose an unacceptable risk.

At each in-person visit after screening (Visits 2-7), patients will undergo depression screening using the PHQ-9. Patients who score ≥ 10 at Visit 2 will need to be further assessed by the investigator for depression and other DSM-5-based diagnoses (per exclusion criterion #26) prior to allocation of study drug. Patients who report an answer of 1+ to the question of being bothered in the last two weeks of "Thoughts that you would be better off dead, or of hurting yourself in some way" should be further assessed with the C-SSRS. If the C-SSRS confirms suicidal ideation or behavior, the patient must be excluded from trial participation. In the event that a patient reports non-suicidal self-injurious behavior on the C-SSRS, the investigator should assess the event(s), the patient's condition, and the benefits and risks of the patient's continued participation in the study.

Patients with scores ≥ 10 on the PHQ-9 at any time during the study will need to be assessed clinically to determine if they meet criteria for a DSM-5-based diagnosis. If criteria are met for a DSM-5-based diagnosis, the investigator should assess the benefits and risks of the patient continuing participation in the study.

There will be ongoing monitoring of adverse events associated with mood disorders (see also Section 2.3.1).

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency of Collecting Adverse Event and Serious Adverse Event Information

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention (ie, the safety reporting period). 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 intervention.

All serious adverse events will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event after conclusion of the study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse reports are provided in Appendix 3.

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 participant is the preferred method to inquire about adverse event occurrences.

The participant's eDiary entries 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 this instrument, proper follow-up with the participant 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.

8.3.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All serious adverse events and adverse events of clinical interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted. Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will review and then file it along with the investigator brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy Reporting

Details of all pregnancies will be collected after the start of study intervention and until the follow-up visit/EOT (Visit 7) (see Schedule of Activities, Table 1).

If a pregnancy is reported, study intervention should be withdrawn immediately, and the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

8.3.6. Adverse Events of Clinical Interest

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

8.3.6.1. Liver Function Tests ≥ 3 × Upper Limit of Normal

Any ALT or AST elevation of this degree or greater occurring during the safety reporting period (the treatment period through 14 days after the last dose of study intervention) should be reported to the sponsor using the safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. Additional instructions for evaluating participants with an increase in ALT or AST ≥ 3 × ULN may be found in Appendix 5.

8.3.6.1.1. Criteria for Temporary Withholding of Study Intervention 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 intervention should be immediately withheld with appropriate clinical follow-up (including repeat laboratory tests, until the participant's laboratory profile has returned to normal/baseline status), and the event reported per Section 8.3.6 and as a serious adverse event if serious adverse event criteria met, including the underlying diagnosis, as available:

- ALT or AST > 8 × ULN; or
- ALT or AST > 5 × ULN and persists for more than 2 weeks; or
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5; or
- ALT or AST > 3 × 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.

8.3.6.1.2. Criteria for Permanent Discontinuation of Study Intervention in Association with Liver Test Abnormalities

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

1. ALT or AST increases to ≥ 3 × ULN; AND
2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × 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 intervention treatment should be withheld or permanently discontinued as appropriate for the safety of the participant.

8.3.6.2. Bone Fracture Events During the Treatment Period

Bone fractures that occur during the safety reporting period should be reported to the sponsor using the safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. See Appendix 6 for further instructions on reporting.

For fractures that occur during the post-treatment follow-up period, see Section 8.3.8.

8.3.7. Adverse Events Related to Menstrual Bleeding

To ensure consistent reporting, the terms below should be used when participants report alterations from their usual menstrual bleeding pattern that meet adverse event reporting criteria. Select the term that most closely reflects both the volume of the menstrual flow and the frequency/duration/regularity of the bleeding episodes.

- Amenorrhea: Absence of menstrual bleeding

- Spotting Vaginal: Spotting regardless of the frequency/duration/regularity
- Oligomenorrhea: Infrequent bleeding/light or normal volume
- Polymenorrhea: Frequent bleeding/light or normal volume
- Menorrhagia: infrequent or regular frequency bleeding/ heavy volume OR prolonged bleeding regardless of flow volume
- Hypomenorrhea: regular frequency/light volume
- Metrorrhagia: irregular frequency/light or normal volume
- Menometrorrhagia: irregular bleeding/heavy volume

8.3.8. Post-Treatment Follow-Up Period

Treatment-emergent adverse event reporting will complete after the 14-day safety follow-up period. During the post-treatment follow-up period, the sponsor will continue to collect information on events related to bone health, eg, DXA measurements and fracture events. Clinical information for a fracture occurring during the post-treatment follow-up period should be reported using the safety report form within 24 hours of the study site personnel's knowledge of the event even if the event does not meet serious adverse event criteria (see Appendix 6).

8.4. Treatment of Overdose

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

For this study, the protocol-specified dose of relugolix combination therapy is one tablet once daily. 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 participant for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a safety report form according to Appendix 3 whether or not the overdose is associated with an adverse event;
- Document the quantity of the excess dose as well as the duration of the overdosing in the Overdose eCRF page.

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Health Economics/ Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no hypothesis associated with the primary endpoint.

9.2. Sample Size Determination

9.2.1. Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 10,000 menstrual cycles of drug exposure in participants 18 to 50 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of 13 28-day cycles;
- 40% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 5 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

9.2.2. Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% confidence interval (CI) for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is

assumed with parameter $\theta = 100\lambda T$ where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100-woman years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with FDA Guidance for Industry (FDA 2019).

At least 10,000 menstrual cycles of drug exposure will be achieved. Assuming 70% of menstrual cycles are at-risk and 40% dropout rate (assuming discontinuers will on average contribute 5 cycles of exposure), approximately 1020 participants must be enrolled to achieve at least 7000 at-risk cycles. Additional participants may be enrolled to ensure a minimum of 200 participants completing the study. With 7000 at-risk cycles, the study will have 95% power for the upper limit of the two-sided 95% CI for the Pearl Index to be < 5 in the overall population, assuming that the true Pearl Index is 2 and that a Poisson model is used to achieve the CI.

The study is powered based on the combined patient population of women with uterine fibroids or endometriosis. The study aims to enroll approximately 50% of women with uterine fibroids (with a minimum of 40%) and up to 50% of women with endometriosis(with a minimum of 25%).

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.3. Populations for Analyses

The analysis populations are defined in Table 8.

Table 8: Study MVT-601-050 Analysis Populations

Analysis Population	Description
Enrolled	All participants who have completed the informed consent process, completed screening procedures, and have been allocated to treatment
Intent-to-Treat (ITT)	All participants who receive at least one dose of study intervention
Modified Intent-to-Treat (mITT)	The subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred
Per-Protocol (PP)	The subset of participants in the rITT population with at least one treatment cycle that is also without specific protocol deviations

Restricted Intent-to-Treat (rITT)	The subset of participants included in the ITT population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred

Abbreviations: ICF = informed consent form.

9.4. Statistical Analyses

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be finalized prior to database lock. This section provides a summary of the planned statistical analyses of the endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

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 participants. Categorical data will be summarized by counts and percentages.

The single, final analysis of all efficacy and safety data will occur after approximately 1020 participants have enrolled and been followed for 14 days after cycle 13 or last dose, if not early terminated.

The safety follow-up analysis will occur after participants have completed 12 months post-treatment follow-up, if not early terminated. Safety follow-up analysis will include two post-treatment DXAs to be performed at 6 months and 12 months after the end-of-treatment visit.

9.4.1.1. Handling of Missing Data

At-risk cycles will be considered those cycles in which participants note vaginal intercourse and no birth control methods other than the study drug were used. These two survey questions are asked once in the eDiary at the end of each 28-day cycle. Cycles will not be included as at-risk cycles in the denominator of the PI calculation if the answers to one or both of these survey questions are missing.

If subjects have fewer than 21 days of eDiary entry in a given cycle (< 75% compliance rate), that cycle will not be included in the analysis of bleeding and spotting days. Additionally, a sensitivity analysis will be conducted in which this cycle will not be labeled at-risk and will not be included in the denominator of the PI calculation. Specific rules for handling of missing data will be provided in the Statistical Analysis Plan.

All cycles in which on-treatment pregnancies occur (regardless of missing eDiary entries or missing survey questions) will be counted as at-risk cycles.

For estimating on-treatment BMD percent change from baseline, to account for any missing BMD assessment at a scheduled visit, a mixed-effects model with repeated measures will be fit to derive the least square means and 95% CI at Month 6 and Month 12. This model will also consider potential confounding effects as covariates such as age at baseline, visit, baseline BMD, race, BMI at baseline, as fixed effects using an unstructured variance-covariance matrix.

Further details on the endpoint analyses including sensitivity analysis, handling of missing data, and statistical methods will be provided in the Statistical Analysis Plan.

9.4.2. Evaluable Cycles and Pearl Index Definitions

Evaluable cycles are defined below and will contribute to the denominator for calculating each type of PI.

- At-Risk PI (primary efficacy endpoint): Cycles without use of any other contraceptive methods and with confirmed vaginal intercourse (At-Risk Cycles).
- Gross PI: On-treatment cycles.
- Modified At-Risk PI: Cycles without use of any other contraceptive methods regardless of occurrence of vaginal intercourse.
- Method Failure PI: At-Risk Cycles without major protocol deviations.

9.4.3. Primary Endpoint

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment:

$$\text{Pearl Index (PI)} = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{number of 28-day at-risk cycles of treatment}}$$

There is no hypothesis associated with the primary endpoint. The primary contraceptive efficacy will be assessed by the point estimate of At-Risk PI and corresponding 95% CI. On-treatment pregnancies are pregnancies with an ECD between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the EDD will be ascertained. The ECD will be calculated as:

$$\text{EDD} - 38 \text{ weeks} = \text{ECD}$$

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses or βhCG level.

The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse. The numerator and denominator in the At-Risk PI calculation are slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, as the primary contraceptive efficacy analysis, will be conducted using an rITT population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred. The At-Risk PI will be presented together with the two-sided 95% CI calculated based on a Poisson distribution (Benda et al. 2004).

The primary efficacy endpoint will be assessed by subgroups based on selected baseline characteristics (including age, indication, race, BMI, region, etc.), as appropriate. Details will be included in the Statistical Analysis Plan.

9.4.4. Secondary Endpoints

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution. Specifically:

- The Gross PI will be estimated using the ITT population, defined as participants 18 to 50 years of age at the time of enrollment who have entered the study and have at least one on-treatment cycle.
- The modified PI will be estimated using the modified ITT (mITT) population, defined as the subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred.
- The Method Failure PI will be estimated using the per protocol analysis population, defined as the subset of participants in the rITT population, with at least one treatment cycle that is also without specific protocol deviations. For calculation of the Method Failure PI, only pregnancies with a conception date during at-risk cycles that were also per protocol are included in the numerator.
- Cumulative 1-year pregnancy rate will be calculated on each of the analysis populations by the Kaplan-Meier (KM) survival analysis. All participants will be followed until they either have an outcome of pregnancy or are censored at the time of their last follow-up. The unit of time in the KM analysis will be the cycle, with pregnancies recorded by cycle of conception. Unlike the PI calculations, cycles based on use of adjunctive contraception will not be excluded.

9.4.5. Tertiary/Exploratory Endpoint(s)

Not applicable.

9.4.6. Safety Endpoints

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention treatment, and severity. An adverse event reported more than once for a participant is counted once at the maximum severity or strongest relationship to study intervention treatment when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each 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 bone mineral density lumbar spine (L1-L4), total hip, and femoral neck. The absolute change and percent change from baseline to 6- and 12-month on-treatment time points and associated 95% CIs will be presented for each bone mineral density location. The same analysis will be also performed for the absolute and percent change from baseline to last on-treatment visit (or early termination [ET] visit) to 6- and 12-month post-treatment follow up visits. Additional analyses can be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure, if appropriate.

Bleeding profile, including bleeding intensity and number of bleeding days, will be summarized by descriptive statistics.

9.4.7. Other Analyses

Not applicable.

9.5. Interim Analyses

No formal interim analyses are planned for this study.

9.6. Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) 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 DSMB will be outlined in a separate charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/(independent ethics committee) IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosures

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants undergoing rescreening will sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

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

Data Quality Assurance

Documentation Accountability

- All participant data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the completion of the informed consent process by the first participant and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. CLINICAL LABORATORY TESTS

- All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the protocol Schedule of Activities (see Table 1).
- Laboratory requisition forms must be completed, and samples must be clearly labeled with the Participant 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 9.
- Investigators must document their review of each laboratory safety report.
- Local laboratory results are only required in the event that central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9: Study MVT-601-050 Protocol-Required Safety Laboratory Assessments

Chemistry	**Hematology**	**Other**
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin	WBC Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Serum Pregnancy Test (βhCG) Urine Pregnancy Test Hemoglobin A1C International normalized ratio (INR) Thyroid Stimulating Hormone (TSH) Parathyroid hormone (PTH) 25-Hydroxyvitamin D (Vitamin D3)
Liver tests: Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase LDH	**Lipid Profile**	**Serology**
	Total Cholesterol Low Density Lipoprotein High-Density Lipoprotein Triglycerides	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody Hepatitis D antibody Hepatitis E antibody Epstein-Barr Virus

Abbreviations: βhCG= beta human chorionic gonadotropin; LDH = lactic acid dehydrogenase; RBC = red blood cells; WBC = white blood cell.

APPENDIX 3. ADVERSE EVENTS DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an adverse event per definition above, then it cannot be a serious adverse event even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient 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 disability/incapacity • 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 with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgement should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include 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.

Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and/or Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event or serious adverse event information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or their representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event or serious adverse event.

Assessment of Intensity

The investigator will make an assessment of intensity for each adverse event and serious adverse event reported during the treatment period and for 14 days after according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). For terms not specified with the CTCAE, the criteria below should be used to determine the grade severity:

Severity 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

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each adverse event.
A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each adverse event, the investigator **must** document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to PHV-Myovant@quintiles.com. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event to PHV-Myovant@quintiles.com.

The investigator may change his/her opinion of causality in light of follow-up information and send a Safety Report Form follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions are to be used for the relationship of the adverse event to study intervention:

- **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 re-administration (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.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to PHV-Myovant@quintiles.com within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to IQVIA RDS, Inc. via Paper CRF

- E-mail transmission of the Safety Report Form paper CRF is the preferred method to transmit this information to the global safety database.
- In rare circumstances and in the absence of e-mail or e-fax equipment, notification by telephone is acceptable with a copy of the Safety Report Form data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Safety Report Form within the designated reporting time frames.
- Contacts for serious adverse event reporting follow:

Using a Safety Report Form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study intervention.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Safety Report Form and is as follows:

Site Location	E-mail (Primary Reporting Method)	Fax Number (Secondary Reporting Method)
All Regions	[redacted]	[redacted]

For questions regarding serious adverse event or adverse event of clinical interest reporting, please call:

- North/South America: [redacted]
- Regional toll-free phone and fax lines distributed separately.

The initial report should include:

- Study number (MVT-601-050)
- Site address and number
- Investigator name
- Participant ID number, sex, and age
- Details of study intervention 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 intervention

If the participant 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 intervention 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, stabilization, the event is otherwise explained, or the participant is lost to follow-up. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

APPENDIX 4. COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the pregnancy report form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be a serious adverse event and will be reported as such.
- Any post-study pregnancy related serious adverse event considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female participant who has an on-treatment pregnancy will discontinue study intervention immediately and return for a Pregnancy visit as described in Section 8.1.5.4.

APPENDIX 5. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Study intervention (relugolix combination therapy) should be withheld for any liver test abnormality listed in Section 8.3.6, 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 Table 10, and per the investigations in Table 11. If close monitoring is not possible, study intervention should be withheld even if the results do not meet the criteria for withholding in Section 8.3.6.

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

Table 10: Study MVT-601-050 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (ALT, AST, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If ALT or AST ≥ 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 participant is asymptomatic	Frequency may decrease

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

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

Table 11: Study MVT-601-050 Investigations and 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 Table 10; • 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).

Abbreviations: CBC = complete blood count; INR = International normalized ratio.
Note: If the first follow-up test does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

APPENDIX 6. FRACTURES: INFORMATION FOR REPORTING

Study intervention should be discontinued permanently for any fragility fracture (defined as a fracture occurring as a result of a fall from a standing height or less in the absence of major trauma). The classification of fragility fracture specifically excludes fractures of fingers, toes, face, or skull. Any fracture that occurs during the study should be reported to the sponsor using the designated safety report form.

The following information should be reported to the sponsor:

- Bone(s) that was/were fractured;
- Description of the event leading to the fracture and classification of the fracture as either non-fragility or fragility fracture (see definition above);
- Full assessment of patient's risk factors for fracture and/or confounders for bone loss/fracture;
- Treatment required (none, conservative, surgery, etc.);
- Evidence of healing, if any.

APPENDIX 7. BREAST IMAGING REPORTING AND DATA SYSTEM

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.	Short-interval (6-month) follow-up imaging or continued surveillance mammography.
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 8. VALIDATED TOOLS FOR DEPRESSION AND SUICIDALITY SCREENING

Scoring of PHQ-9
Note: the PHQ-9 is administered via a paper questionnaire

PHQ-9 Score	Depression Severity	Actions
0-4	None-minimal	If patient answers 1+ on question 9, complete C-SSRS
5-9	Mild	If patient answers 1+ on question 9, complete C-SSRS
10-14	Moderate	Evaluate patient for DSM-5-based diagnoses, consider risks and benefits of continued participation in the study If patient answers 1+ on question 9, complete C-SSRS
15-19	Moderately Severe	Evaluate patient for DSM-5-based diagnoses, consider risks and benefits of continued participation in the study If patient answers 1+ on question 9, complete C-SSRS
20-27	Severe	Evaluate patient for DSM-5-based diagnoses, consider risks and benefits of continued participation in the study If patient answers 1+ on question 9, complete C-SSRS

PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

(For office coding: Total Score _____ = _____ + _____ +_____)

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
❑	❑	❑	❑

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Columbia Suicide Severity Rating Scale: For Use at Baseline

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** **No** ☐ ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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Columbia Suicide Severity Rating Scale: For Use at Visits 2-7 (see Section 8.2.8)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

APPENDIX 9. GUIDANCE FOR STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The novel coronavirus 2019 (COVID-19) pandemic has impacted the conduct of clinical trials globally. Regional quarantine laws, travel restrictions, and site closures present challenges to normal study conduct and may lead to missed study visits or procedures or an interruption to a patient's study drug supply.

Myovant Sciences has thoroughly reviewed guidance documents from various country and regional regulatory agencies and has put mitigation plans in place to ensure that the safety of patients is maintained, the study continues to be conducted in compliance with Good Clinical Practice (GCP), and risks to the integrity of the study are minimized. These plans will remain in place through the duration of the COVID-19 pandemic.

Safety During the COVID-19 Pandemic

Protecting study patients, investigational site staff and clinical service providers involved in Myovant Sciences clinical studies from activities that may unnecessarily increase the risk of contracting COVID-19 is of utmost importance. Regulations and policies instituted for safety purposes during the COVID-19 pandemic at the institutional, local, country, and regional level should be adhered to.

Protocol Adherence

Wherever possible and safe, study visits and procedures must be performed as outlined in the protocol to ensure patient safety and to maintain the integrity and interpretability of the study data. While modifications to normal study conduct may, in some cases, be necessary and unavoidable, they must be documented and reported where in conflict with the study protocol and this guidance. Deviations from the protocol will be documented, but those resulting specifically from the COVID-19 pandemic will be marked as such. All deviations resulting from the COVID-19 pandemic will be summarized in the clinical study report.

Visit Schedules and Study Procedures

Local policies, institutional restrictions, and/or patient ability/willingness to make site visits may curtail the ability to adhere to the in-person, on-site visit schedule required by the protocol. Investigators at clinical sites should evaluate the appropriateness of an on-site study visit during the COVID-19 pandemic.

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, as close to the visit target date as possible, taking all measures to prevent contracting COVID-19.

- All protocol-required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, Investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.
- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of

the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the Myovant medical monitor for consultation, as necessary.

If the clinical study site is closed or the patient is unable/unwilling to attend on-site study visits due to the COVID-19 pandemic, alternative methods for completing assessments (eg, phone contact or virtual visit) should be implemented.

- Investigators must assess and evaluate the patient's continued participation and dosing with limited safety assessment.
- At a minimum, investigational site staff should make every attempt to contact the patient via telephone when an expected visit is due or missed to assess for adverse events, document concomitant medications, and study drug dosing since the last study visit.
- If the safety blood draws cannot be performed through the central laboratory per protocol, the investigator may advise the patient to have blood drawn at a local laboratory if there is a safety concern. If two consecutive study visits are missed and the patient is unable to return to the site, the investigator should advise the patient to have protocol-specified safety labs completed at a local laboratory to assess for any safety concerns. In both cases, the local laboratory results should be documented in the eCRF.
- Investigational sites should report all serious adverse events, adverse events of clinical interest, overdose, and pregnancy that the patient reports during these calls within 24 hours of awareness.
- Patients should be reminded of the importance of taking study drug daily or of using back-up contraception if study drug is interrupted.
- Study patients should continue to complete their daily eDiary, even if they run out of study drug, and site staff should motivate them to do so.

Patients should have the contact details of the investigational site medical staff to report any medical issues, including adverse events they may experience in real time.

As soon as the study patients are able to return to the investigational site for an on-site visit, they should do so. The next scheduled visit should occur on the target date as per the Schedule of Activities (see Table 1).

Study Participant Study Drug Supply

If a regional lockdown, travel restrictions, or site closure is imminent due to the COVID-19 pandemic, sites are encouraged to dispense additional study drug at an expected study visit or request patients to return for an unscheduled visit for additional study drug dispensation so patients have sufficient supply until their next upcoming visit. Patients should be instructed to contact the site to report any medical issues they may experience and site staff should communicate with the patients to determine if it is appropriate for the patient to continue dosing with study drug if/when in-person study visits are not possible.

For cases where study patients are unable to visit the investigational site to pick up study drug, a direct-to-patient delivery of study drug by site staff or shipment via contracted courier may be possible. Consent authorizing direct-to-patient supply will be obtained. Sites should defer to national guidance on how this will occur. Where permitted by national guidance, verbal consent will be taken via telephone or video call and noted in the patient's source file. Where required, by national guidance, this will be followed up with written consent during the next clinic visit. Every effort will be made to obtain the patient's written consent for direct-to-patient delivery prior to delivery or shipment, where this is required by national guidance.

In the event that none of the above are possible for participants to continue taking study medication, a patient may need to be discontinued per the study protocol. Such decisions will be made on a case-by-case basis in discussion with the investigator and medical monitor.

On-Site Study Monitoring Restrictions

In the event study monitors/clinical research associates are not allowed to travel and/or return to a clinical site to monitor and source document verify study data, Myovant has developed plans to ensure monitors:

- Remotely verify source documentation as much data as reasonably possible without burdening sites, if allowed by the study site and country regulations, focusing on pages key to the interpretability of the study and the safety of participants.
- Remotely monitor study data through cross checking of various systems housing patient data against what is captured in the eCRFs.

Additional guidance on conducting clinical trials during the COVID-19 pandemic may be found in the following documents released by Regional Health Authorities, which may be updated (updates supersede the versions listed here):

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated 27 Jan 2021);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – Version 4 04 Feb 2021.

APPENDIX 10. ABBREVIATIONS

List of Abbreviations and Definition of Terms

Abbreviation	Definition
βhCG	beta human chorionic gonadotropin
AGUS	atypical glandular cells of undetermined significance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATE	arterial thrombotic or thromboembolic event
BMD	bone mineral density
BMI	body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CKD	chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	novel coronavirus 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
DXA	dual-energy X-ray absorptiometry
E2	estradiol
ECD	estimated conception date
eCRF	electronic case report form
EDD	estimated date of delivery
eDiary	electronic diary
EHP-30	Endometriosis Health Profile-30
EOT	end-of-treatment
ET	early termination
FDA	Food and Drug Administration
FDC	fixed-dose combination (tablet)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HPV	human papilloma virus
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-response system
KM	Kaplan Meier
LH	luteinizing hormone
LSIL	low-grade squamous intraepithelial lesion
MBL	menstrual blood loss
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified ITT
NETA	norethindrone acetate
PHQ-9	Patient Health Questionnaire-9
PI	Pearl Index
PTFU	post-treatment follow-up
PTH	parathyroid hormone
QD	once daily
QTcF	QTc corrected using Fridericia's formula
rITT	restricted intent-to-treat
STD	sexually transmitted disease
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

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Clinical Study Protocol

Protocol Title:	A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy
Protocol Number:	MVT-601-050
Amendment Number:	3
Compound:	Relugolix Combination Therapy (relugolix, estradiol, norethindrone acetate)
Study Phase:	Phase 3
Short Title:	A Phase 3 Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis who are at Risk for Pregnancy
Sponsor Name:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Agency Identifier Numbers:	IND 131161
Approval Date:	Original: 12 Aug 2020 Amendment 1: 21 Dec 2020 Amendment 2: 07 Jul 2021 Amendment 3: 15 Sep 2021

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy

Protocol Number: MVT-601-050 Amendment 3

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

DocuSigned by:

[redacted]

15-Sep-2021 | 1:33 PM PDT

Date

15-Sep-2021 | 1:52 PM PDT

Date

15-Sep-2021 | 10:31 AM PDT

Date

15-Sep-2021 | 10:27 AM PDT

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)	Principal Investigator Signature
Clinical Site Number	Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy

Short Title: A Phase 3 Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Fibroids or Endometriosis Who Are at Risk for Pregnancy

Protocol Number: MVT-601-050

Location: North America

Study Centers: Approximately 100 sites

Study Phase: Phase 3

Target Population: Women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy

Rationale:

This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy. Myovant is developing relugolix combination therapy for the indications of the management of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis. Both conditions are prevalent in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy of relugolix combination therapy in treatment of symptoms associated with endometriosis or uterine fibroids, or the safety of patients undergoing treatment with relugolix combination therapy. By quantifying the contraceptive effectiveness of relugolix combination therapy (using the Pearl Index [PI]), results from this study will provide evidence for patients and their healthcare providers to make an informed decision about the need to use additional nonhormonal contraception while being treated with relugolix combination therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: $PI = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy:	
Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
"Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
"Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
Contraceptive efficacy in various populations and analysis sets.	Cumulative 1-year pregnancy rates.
Safety	
To describe the safety of relugolix combination therapy.	Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
To evaluate change in bone mineral density during treatment with relugolix combination therapy.	Percent change in bone mineral density from baseline to 6 and 12 months on-treatment at lumbar spine (L1-L4), total hip, and femoral neck.

Objectives	Endpoints
To evaluate post-treatment change in bone mineral density.	Percent change from baseline and 12 months on-treatment (or Early Termination) to the 6-month and 12-month post-treatment time points at lumbar spine (L1-L4), total hip, and femoral neck.
To estimate discontinuation rate.	Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

Overall Design:

Study MVT-601-050 is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy (relugolix 40 mg, estradiol [E2] 1 mg, and norethindrone acetate [NETA] 0.5 mg). Approximately 1020 sexually active women with uterine fibroids or endometriosis who are 18 to 50 years of age and will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

The study period consists of a Screening Period (Visit 1), a 52-week Treatment Period (Visits 2 to 6), a 14-day post-treatment Safety Follow-Up Period (Visit 7), as well as a 12-month Post-Treatment Follow-Up (PTFU) period during which bone mineral density (BMD) is monitored.

Participant eligibility will be determined based on assessments performed at Visit 1. The participant's medical and gynecological history (including contraception and use of prior medications) will be reviewed and a diagnosis of either uterine fibroids with heavy menstrual bleeding or endometriosis with associated pain will be confirmed (see inclusion criteria). An ultrasound may be performed to confirm diagnosis of uterine fibroids if there is no previous documented record from the past two years. Height, weight, and vital signs will be measured; and physical, gynecological, and breast examinations will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy, and participants will be screened for the sexually transmitted diseases (STDs) gonorrhea and chlamydia. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening for suicidal ideation will be performed using the Columbia – Suicide Severity Rating Scale (C-SSRS). Participants who are 40 or older will need to undergo a screening mammogram (see Appendix 7).

Participants who meet all eligibility criteria will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Prior to initiation of treatment with relugolix combination therapy on Day 1 (Visit 2), patients will need to undergo a baseline assessment of bone mineral density via dual-energy X-ray absorptiometry (DXA) scan. On Day 1 (Visit 2), continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be

measured to determine baseline values. Participants must have a negative urine pregnancy test. Participants will also receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Finally, study medication will be dispensed, together with instructions for administration and back-up contraception, if applicable. The window for initiating dosing with relugolix combination therapy also depends upon contraceptive status. If Visit 2 occurs within the correct window, dosing may begin at Visit 2. Otherwise, the participant will initiate dosing at home when the appropriate window is reached and after another negative urine pregnancy test result is recorded in the eDiary. Thereafter, continuous treatment with relugolix combination therapy will be taken for 13 consecutive 28-day treatment cycles.

Throughout the Treatment Period, compliance with study intervention administration will be recorded daily in the eDiary. At the completion of each 28-day treatment cycle, the participant will record the results of a urine pregnancy test and indicate whether intercourse or use of additional contraception occurred during the previous 28-day treatment cycle. Each treatment cycle starts with the result of a home pregnancy test, the result of which must be negative and must be entered in the eDiary for a participant to continue in the study. Assessments of safety (physical, gynecological, and breast examinations; laboratory assessments; vital signs, etc.) will be performed throughout the study. DXA scans will be performed at 6-month intervals during treatment and the post-treatment follow-up period. Telephone visits to assess compliance and safety will be performed approximately 6 weeks following each on-site visit during the treatment period.

Fourteen days after discontinuation of treatment, a follow-up/end-of-treatment (EOT) visit (Visit 7) will be conducted. All assessments done at on-treatment visits will be repeated and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for selected serum chemistry assessments, including β-hCG to determine pregnancy and safety assessments will be performed. A 12-month on-treatment DXA will be performed no later than the time of this visit. A mammogram will be performed, if indicated. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

Two PTFU DXAs will be performed at 6 months and 12 months after the end-of-treatment visit. Clinical laboratory tests (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphate) will be performed if bone mineral density loss meets pre-specified criteria. Any participant who has an on-treatment pregnancy will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Inclusion and Exclusion Criteria:

Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 50 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;

4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a diagnosis of uterine fibroids or endometriosis meeting *either* of the below criteria:
    a. Diagnosis of uterine fibroids by confirmation of ultrasound performed in the last 2 years (submucosal fibroids > 50% intracavitary are excluded) and patient report of heavy menstrual bleeding affecting quality of life.

       Note: If an ultrasound report from the last 2 years cannot be located, the participant should undergo transvaginal ultrasound at the time of screening to confirm the presence of one or more uterine fibroids.

    b. Diagnosis of endometriosis and has had, prior to signing the informed consent form, surgical or direct visualization (laparoscopy or laparotomy) and/or histopathologic confirmation of endometriosis, and during the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and/or during non-menstrual portion of the cycle in the prior month;
6. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
7. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through end of treatment;
8. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
9. Has body mass index (BMI) $\geq$ 18 kg/m^2;
10. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

<u>Exclusion Criteria</u>

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:
    a. Vascular disease (eg, cerebrovascular disease, coronary artery disease, peripheral vascular disease);
    b. Women over 35 who smoke;
    c. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation);

d. Inherited or acquired hypercoagulopathies, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant);

   Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

   Note: The specific reasons for exclusion should be documented in the interactive web-response system (IWRS).

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Malabsorptive disease (including, but not limited to, inflammatory bowel disease and gastric bypass surgery);
11. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

    Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

12. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
13. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

14. Has a known history of infertility or subfertility (examples include but are not limited to prior ectopic pregnancy, prior surgery of fallopian tube, prior imaging or procedure suggesting non-patent fallopian tube, history of infertility workup or treatments);
15. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
16. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.
17. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, intermenstrual/bleeding between menstrual periods, bleeding from a cervical polyp, recurrent bleeding after intercourse);
18. Has a known submucosal fibroid (> 50% intracavitary);
19. Women with a diagnosis of endometriosis who have had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis.

Other Conditions/Disorders

20. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);

21. Has known human immunodeficiency virus (HIV) infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
22. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
23. Has known BRCA mutation or other mutation associated with increased risk of breast cancer;
24. 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;
25. History of suicidal ideation or suicidal behavior, or confirmed "yes" to any question (with exception of non-suicidal self-injurious behavior, unless deemed as an unacceptable risk by the investigator) on the C-SSRS;
26. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders (based on Diagnostic and Statistical Manual of Mental Disorders 5 [DSM-5] criteria) who have been unstable or not well controlled based on the investigator or mental health professional's judgement, 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 treatment period should not be enrolled;
27. Has a hepatic hemangioma, or has a history of cholestasis with prior estrogen use or during pregnancy;
28. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
29. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
30. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

31. Has a known or suspected pregnancy;
32. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
33. Is breastfeeding or has breastfed in the last year.

At risk of bone loss or unable to be monitored for changes in bone density

34. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
35. Has a bone mineral density Z-score ≤ -2.0 at lumbar spine, femoral neck, or total hip during the screening period;
36. Screening 25-OH-Vitamin D level < 12 ng/mL (patients with vitamin D deficiency with levels 12-19 ng/mL are permitted if supplementing with vitamin D);

    Note: If patients fail screening because of vitamin D levels, they may begin supplementing with vitamin D at the discretion of the treating clinician and be re-screened eight weeks later.
37. Has a history of or currently has osteoporosis, or other metabolic bone disease, collagen vascular disease, chronic kidney disease (CKD) stage 3 or greater with glomerular filtration rate (GFR) < 60 mL/min/m^2 using Modification of Diet in Renal Disease (MDRD) method, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, hyperthyroidism, anorexia nervosa, abnormal bone mineral metabolism (eg, hypophosphatemia), or low traumatic (fragility) fracture. 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;
38. Past history of use or current use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
39. Prior use of depo-medroxyprogesterone acetate for a treatment period > 2 years.

Concomitant and Recent Medications/Devices

40. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
41. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
42. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein);
43. Has used chronic glucocorticoids that are oral, parenteral, inhaled (prednisone equivalents of ≥ 2.5mg daily for ≥ 3 months) in 12 months prior to the study. Women with epidural or spinal glucocorticoid use at any dose in the last 12 months are excluded.

Miscellaneous

44. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

Disclosure Statement

This is a single arm, open-label study to evaluate the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy.

Number of Participants:

Approximately 1020 participants will be enrolled. The sample size has been set to attain at least 10,000 treatment cycles and 7000 at-risk treatment cycles for pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse) in participants 18 to 50 years of age at the time of enrollment (see Section 9.2). Additional participants may be enrolled to ensure a minimum of 200 participants completing the study. The enrollment aim is approximately 50% of participants with uterine fibroids (with a minimum of 40%), and approximately 50% of participants with endometriosis (with a minimum of 25%).

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study but do not participate in the study are not considered enrolled.

Intervention Groups and Duration:

Relugolix combination therapy (relugolix 40 mg, E2 1 mg, and NETA 0.5 mg) as a fixed-dose combination tablet is to be taken orally QD at approximately the same time each day. Relugolix combination therapy treatment is continuous; that is, a tablet is to be taken daily for the entire duration of the treatment period, without a drug-free interval.

Study intervention will be self-administered during 13 consecutive 28-day treatment periods ("Cycles"), for a total duration of 52 weeks.

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

Participants may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove participants from therapy under this protocol for reasons of safety and/or lack of compliance, as discussed below. Participants removed from study intervention for any reason will, if possible, undergo assessments for an early termination visit (see Schedule of Activities, Section 1.3), then return again approximately 14 days after the end of treatment (ie, after the participant's last dose of study intervention). If the patient has provided consent, she will be recommended to undergo PTFU BMD assessments with DXA and collection of blood samples for clinical laboratory tests at 6 and 12 months (if meeting prespecified criteria).

Criteria for Evaluation:

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the estimated date of delivery (EDD) will be ascertained. The estimated conception date (ECD) will be calculated as:

- EDD − 38 weeks = ECD

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses, or β-hCG level.

Statistical Methods:

Contraceptive Efficacy

This study has one primary endpoint, the At-Risk PI, calculated on the basis of the number of on-treatment pregnancies in the numerator and the number of at-risk cycles of exposure in the denominator. The numerator and denominator are thus slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, the primary contraceptive efficacy analysis, will be conducted using a restricted intent-to-treat (rITT) population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred (ie, a treatment cycle containing an ECD for a pregnancy). The At-Risk PI will be presented together with the two-sided 95% confidence interval (CI) calculated based on a Poisson distribution (Benda et al. 2004). There is no hypothesis associated with the primary endpoint.

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution.

Safety

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, laboratory evaluations, mammogram, and DXA scans.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention, and severity. An adverse event reported more than once for a participant will be counted once at the maximum severity or strongest relationship to study intervention when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Mammograms will be obtained at baseline and then at the end of treatment for women who are age 40 or older.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the baseline, 6- and 12-month on-treatment time points, as well as at 6-and 12-months post-treatment (hereafter referred to as PTFU Month 6 and PTFU Month 12). All patients who discontinue treatment prior to completing 13 cycles of study medication will still undergo PTFU Month 6 and PTFU Month 12 DXA assessments. The percent change in BMD will be measured at all time points relative to the baseline value.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

Sample Size Determination

Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 10,000 treatment cycles in participants 18 to 50 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of thirteen 28-day treatment cycles;
- 40% of participants will discontinue the study;
- Participants who discontinue will, on average, contribute 5 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% CI for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$, where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100 woman-years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion

of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with the FDA Guidance for Industry (FDA 2019).

Assuming 70% of menstrual cycles are at-risk and a 40% dropout rate (assuming participants who discontinue will on average contribute 5 cycles of exposure), approximately 1020 participants must be enrolled to achieve at least 7000 at-risk cycles. A minimum of 200 participants completing the study will be ensured. With 7000 at-risk cycles, the study will have 95% power for the upper limit of the two-sided 95% CI for the Pearl Index to be < 5 in the overall population, assuming that the true Pearl Index is 2 and that a Poisson model is used to achieve the CI. Myovant has powered the study based on the combined population of women with uterine fibroids or endometriosis. The study aims to enroll approximately 50% of women with uterine fibroids (with a minimum of 40%) and approximately 50% of women with endometriosis (with a minimum of 25%).

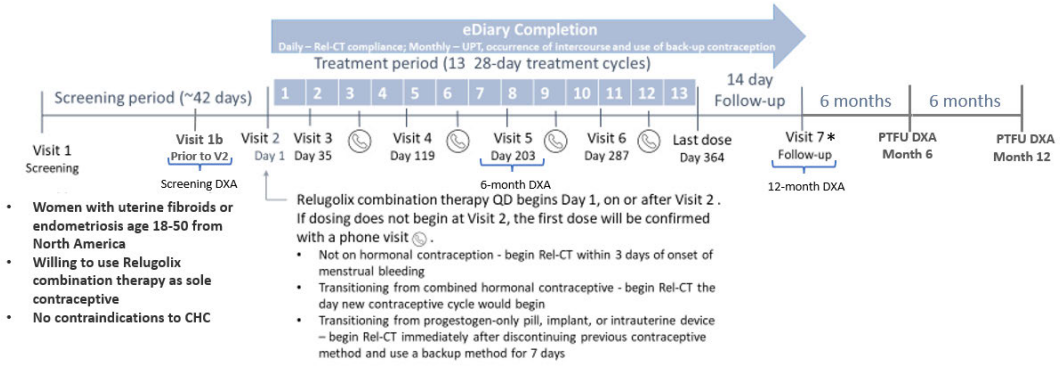
Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) 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 DSMB will be outlined in a separate charter.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: MVT-601-050 Study Schematic



Abbreviations: CHC = combined hormonal contraceptive; DXA = dual energy X-ray absorptiometry; E2 = estradiol; eDiary = electronic diary; NETA = norethindrone acetate; PTFU = post-treatment follow-up; QD = once daily; Rel-CT = relugolix combination therapy (relugolix 40 mg, E2 1 mg, NETA 0.5 mg); UPT = urine pregnancy test.
* or 14 days after the last dose.
Note: During the treatment period Visits occur approximately 7 days after the end of the previous cycle. Phone visits occur approximately 6 weeks after the subsequent Visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities for MVT-601-050

Trial Period	**Screening**		**Allocation**	**Treatment Period**							
Visit	**V1**	**V1B**	**V2[a]**	**V3**	**P3**	**V4**	**P4**	**V5**	**P5**	**V6**	**P6**
Visit Timing	**−42 D**	**-30 D to -15 D**	**On or prior to D1[b]**	**7 days after Cycle 1**	**~6 wks after V3**	**~7 days after Cycle 4**	**~6 wks after V4**	**7 days after Cycle 7**	**~6 wks after V5**	**7 days after Cycle 10**	**~6 wks after V6**
Day of Study Intervention Treatment[c]			**D 1[d]**	**D 35**	**D 77**	**D 119**	**D 161**	**D 203**	**D 245**	**D 287**	**D 329**
Informed Consent	X										
Inclusion/Exclusion Criteria	X		X								
Medical History	X										
Gynecological History	X										
Prior and Concomitant Medication	X		X	X	X	X	X	X	X	X	X
Contraceptive History	X		X								
Columbia Suicide Severity Rating Scale[w]	X		X[x]	X[x]		X[x]		X[x]		X[x]	
Patient Health Questionnaire-9[x]			X	X		X		X		X	
Dispense eDiary			X								
eDiary Training/Re-Training[e]			X	X	X	X	X	X	X	X	X
Dispense Study Intervention			X	X		X		X		X	
eDiary Compliance/Data Review				X	X	X	X	X	X	X	X
Drug Accountability[f]				X		X		X		X	
Contraceptive Counseling										X[g]	X[g]
Physical Examination[h,i]	X										
GYN & Breast Examination[i]	X										
Height	X										
Weight, Vital Signs (HR, BP)	X		X	X		X		X		X	
Adverse Event Monitoring	X		X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests[j]	X			X		X		X		X	
Gonorrhea/Chlamydia Test	X										
Cervical Cytology[k]	X										
Mammogram[u]	X										

Serum β-hCG[l]	X										
Urine Pregnancy Test[m]			X	X		X		X		X	
Transvaginal ultrasound[v]	X										
Bone densitometry[r]		X[s]						X		X[t]	

Table 1: Schedule of Activities for MVT-601-050 (Continued)

Trial Period	**Post-Treatment Period**				**Unscheduled**
Visit	**Follow-Up/ EOT (V7)[n]/ Early Termination**	**6-months Post-treatment (PTFU 6-month)**	**12-months Post-treatment (PTFU 12-month)**	**Pregnancy**	
Visit Timing	**14 days after Cycle 13 or Last Dose**	**(+/- 30 days)**	**(+/- 30 days)**	**Upon diagnosis**	
Day of Study Intervention Treatment[c]	**D378**			**NA**	**NA**
Informed Consent					
Inclusion/Exclusion Criteria					
Medical History		X[y]	X[y]		
Gynecological History					
Prior and Concomitant Medication	X	X[y]	X[y]	X	X
Contraceptive History		X[y]	X[y]		
Columbia Suicide Severity Rating Scale[w]	X[x]				X[x]
Patient Health Questionnaire-9[x]	X				X
Dispense eDiary					
eDiary Training/Re-Training[e]					X[p]
Dispense Study Medication					X[p]
eDiary Compliance/Data Review	X			X	X[p]
Drug Accountability[f]	X			X	X[p,q]
Contraceptive Counseling	X[g]				
Physical Examination[h,i]	X			X	X[p]
GYN & Breast Examination[i]	X			X	X[p]
Height					X[p]
Weight, Vital Signs (HR, BP)	X			X	X[p]
Adverse Event Review	X			X	X
Clinical Laboratory Tests[j]	X	X	X	X	X[p]
Gonorrhea/Chlamydia Test					X[p]
Cervical Cytology[k]					X[p]
Mammogram[u]	X				
Serum β-hCG[l]	X			X	X[p]

Urine Pregnancy Test[m]	X	X	X		X[p]
Transvaginal ultrasound[v]				X[o]	
Bone densitometry[r]	X[t]	X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AGC = atypical glandular cells; AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; ALT = alanine transaminase; ASC-H = atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; AST = aspartate transaminase; BP = blood pressure; D = day(s); EDD = estimated date of delivery; eDiary = electronic diary; EOT = end-of-treatment; GGT = gamma-glutamyl transferase; GYN gynecologic; HPV = human papilloma virus; HR = heart rate; HSIL = high-grade squamous intraepithelial lesion; LDH = lactic dehydrogenase; LSIL = low-grade squamous intraepithelial lesion; NA= not applicable; P = phone contact; V = visit.

a. The timing of Visit 2 depends on contraceptive status at screening and the need for washout. Visit 2 should occur after screening tests results indicating eligibility are available.
b. Study intervention dosing (Day 1) occurs during the allocation period (Visit 2). The timing of Day 1 may vary based on the following:
    - For participants not using any prior contraceptive method or using barrier contraception Day 1 must occur within 3 days of the onset of menses and after a negative urine pregnancy test has been recorded in the participant's eDiary. If Visit 2 occurs within 3 days of the onset of menses, the participant will begin her first treatment cycle of relugolix combination therapy dosing at the study visit. If the visit is not within this window, dosing will begin once the participant reports the onset of the next menses, followed by entry of a negative urine pregnancy test result in the eDiary. The eDiary will then instruct the participant to take and record the first dose of study intervention.
    - For participants transitioning from combined hormonal contraceptive pills, patches, or rings: Day 1 is the day she would normally initiate a new contraceptive cycle. If Visit 2 cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.
    - For participants transitioning from progestin-only pills: Visit 2/Day 1 must be scheduled the day after completing treatment with the prior method and the participant must use a back-up method for the first 7 days of relugolix combination therapy.
    - For participants using a contraceptive implant or intrauterine device: Visit 2/Day 1 must be scheduled the day the implant or device is removed. The participant must use a back-up contraceptive method for the first 7 days of relugolix combination therapy.
c. Visits should be scheduled on the target day of study intervention treatment as indicated. If this this not feasible, the visit should occur as soon after the target day as possible. Treatment must not be extended beyond Day 364.
d. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact.
e. Initial eDiary training to be performed when eDiary is dispensed. eDiary training for the participant should be performed/reinforced throughout the study.
f. The participant should be asked to bring all study intervention to the clinic for each visit (see Section 6.4).
g. Counseling regarding post-trial contraceptive use should be provided to all participants at Visit 6 and repeated at Phone Visit 6 and Visit 7 (Follow-up/EOT).
h. A complete physical exam will be conducted at Visit 1 and Visit 7 and will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All other physical examinations should focus on signs and symptoms reported by the participant.
i. Physical, gynecologic, and breast examinations should be conducted by a licensed health professional (eg, physician, nurse practitioner, physician assistant).
j. Clinical laboratory tests will include hematology, chemistry with phosphate, lipid profile, thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), vitamin D, and hemoglobin A1C at screening (see Appendix 2). The screening sample must be obtained in the fasted state (no food or drink other than water after midnight). If the screening period is extended by more than 6 weeks for any reason, screening laboratories (chemistry and hematology) should be

repeated prior to administration of the first dose of study intervention. If vitamin D supplementation was started for vitamin D deficiency in the screening period, a vitamin D level should be drawn at Visit 3. Assessments at Visits 3, 4, and 6 will otherwise only include liver function tests (ALT, AST, GGT, total bilirubin, alkaline phosphatase, lactate dehydrogenase). Visits 5 and 7 will include hematology, chemistry, serum β-hCG, and lipid profile (perform TSH, PTH, vitamin D if BMD loss > 3% or Z-score ≤ -2.0 at PTFU Month 6 or Month 12 DXA). If labs are obtained due to bone mineral density loss of > 3% or Z-score ≤ -2.0 in the post-treatment follow-up period, labs will be limited to vitamin D, TSH, PTH, creatinine, calcium, and phosphate.

k. Cervical smear is only applicable to participants 21 years of age and older (or who will become age 21 during the course of the trial). Cervical cytology does not need to be performed if a normal cervical smear (ie, no evidence of ASCUS with high-risk HPV positive, ASC-H, LSIL, HSIL, squamous cell carcinoma, AGUS, AGC-neoplastic or AIS) performed within 18 months of Visit 1 can be documented and the participant does not report a history of abnormal results within the past 3 years. Cervical smear may be performed by a nurse practitioner or physician's assistant if licensed in the state, is trained, and it is within their scope of practice.
l. A serum β-hCG pregnancy test is required at Visit 1 and Visit 7 (Follow-up/EOT). Serum testing should also be performed during the trial if a pregnancy is suspected, or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound).
m. A urine pregnancy test will be performed at each site visit after screening and prior to each DXA at the DXA facility. Additionally, a home urine pregnancy test performed by the participant is required prior to the start of each cycle and the result must be negative to continue. Any positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound, when applicable).
n. Follow-up/EOT visit also to be done in case of early discontinuation. All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention (ie, the safety reporting period).
o. Transvaginal ultrasonography will be performed to determine gestational age/EDD.
p. For an unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
q. eDiary and any remaining drug should be collected by the site at this visit.
r. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading. A screening, 6- and 12-month on-treatment, and post-treatment follow-up (PTFU) Month 6 and Month 12 DXA will be performed within ± 30 days of the recommended time frame. For further details, see Section 8.2.6.
s. DXA should not be completed before normal baseline physical exam, pathology, laboratory studies, and pregnancy test are completed. The DXA should be performed between 30 to 15 days prior to allocation of investigational product to account for the possibility that a repeat scan will need to be performed.
t. The 12-month on-treatment DXA may occur at the end-of-treatment (EOT) visit. If performing the early termination visit, refer to Section 8.2.6.1 for detailed guidance on whether a DXA needs to be performed.
u. For patients ≥ 40 years old at the time of enrollment and at the end of treatment visit, if this occurs ≥ 1 year past last mammogram. Patients who turn 40 during the study should undergo a mammogram at end of treatment.
v. Patients with uterine fibroids for whom an ultrasound report from the last two years cannot be obtained may undergo transvaginal ultrasound at the screening visit to confirm the presence of one or more fibroids.
w. Patients must complete the Columbia Suicide Severity Rating Scale (C-SSRS) at V1 and at onsite visit if required by Section 8.2.8.
x. If review of Patient Health Questionnaire-9 (PHQ-9) shows an answer of 1+ to the question of being bothered in the last two weeks by "Thoughts that you would be better off dead, or of hurting yourself in some way," this requires further assessment for suicidality with the C-SSRS.
y. At the time of the post-treatment follow-up DXA assessments, patients will be asked to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events.

2. INTRODUCTION

Relugolix is a daily, orally active, potent, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) (relugolix combination therapy) for the treatment of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Relugolix competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are considerably reduced, with the reduction in FSH concentrations preventing natural follicular growth and development, limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Further, prevention of an LH surge inhibits ovulation, and therefore the corpus luteum does not develop, which precludes the production and secretion of progesterone into the systemic circulation. Relugolix is combined with E2 1 mg and NETA 0.5 mg to maintain E2 concentrations within a therapeutic range and progesterone/progestin concentrations at low levels, to treat symptoms associated with endometriosis and uterine fibroids while maintaining bone mineral density (BMD) and preventing vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen.

Relugolix combination therapy is intended to provide an effective and well-tolerated option for the long-term treatment of symptoms associated with endometriosis and uterine fibroids. This study will evaluate the efficacy and safety of relugolix combination therapy as a contraceptive in women with a diagnosis of uterine fibroids or endometriosis.

2.1. Study Rationale

Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Uterine fibroids and endometriosis are both prevalent conditions in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy or safety of participants undergoing treatment with relugolix combination therapy for the treatment of symptoms associated with endometriosis or uterine fibroids. This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis.

This study is being conducted in women of reproductive age with endometriosis or uterine fibroids and presumed normal fertility. By determination of the Pearl Index (PI) for relugolix combination therapy (ie, by quantifying the contraceptive effectiveness), the study will provide evidence for participants and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception during treatment with relugolix combination therapy.

2.2. Background

Replicate, randomized, double-blind, placebo-controlled, 24-week phase 3 studies followed by a long-term open-label extension study were conducted within each indication to support marketing approval. Relugolix combination therapy has been approved in the United States as MYFEMBREE® for the management of heavy menstrual bleeding associated with uterine fibroids.

To support the uterine fibroid indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with heavy menstrual bleeding associated with uterine fibroids. Patients with confirmed uterine fibroids with heavy menstrual bleeding were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (Studies MVT-601-3001 [N = 387] and MVT-601-3002 [N = 381]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open label- extension study (MVT-601-3003), designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the uterine fibroid indication.

A statistically greater proportion of women treated with relugolix combination therapy compared to placebo (73.4% vs. 18.9% [$p < 0.0001$] in MVT-601-3001 and 71.2% vs. 14.7%% [$p < 0.0001$] in MVT-601-3002) achieved the primary endpoint of both a menstrual blood loss volume of < 80 mL and at least a 50% reduction from baseline in menstrual blood loss (MBL) volume over the last 35 days of treatment. Six key secondary endpoints related to menstrual blood loss volume, amenorrhea, change in hemoglobin, pain associated with uterine fibroids as measured by a Numerical Rating Scale, and change in patient-reported distress from heavy bleeding, passing of blood clots, and pelvic pressure as assessed by the validated Bleeding and Pelvic Discomfort scale, and change in uterine volume were also met. Relugolix combination therapy maintained BMD at levels comparable to placebo over 24 weeks and was generally well tolerated. Additionally, the long-term extension study MVT-601-3003 demonstrated durability of treatment effect for up to 52 weeks. The overall safety profile of relugolix combination therapy for up to 52 weeks was consistent with that observed over the first 24 weeks with low incidence of vasomotor symptoms and maintenance of BMD over time.

To support the endometriosis indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 1250 premenopausal women with pain associated with endometriosis. Patients with confirmed endometriosis with moderate to severe pain were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (MVT-601-3101 [N = 628] and MVT-601-3102 [N = 622]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3103) designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the endometriosis indication.

Patients receiving relugolix combination therapy achieved both co-primary endpoints by demonstrating clinically-meaningful pain reductions compared to placebo for dysmenorrhea (74.5% vs. 26.9% [$p < 0.0001$] in MVT-601-3101 and 75.2% vs. 30.4% [$p < 0.0001$] in

MVT-601-3102) and for nonmenstrual pelvic pain (58.5% vs. 39.6% [p < 0.0001] in MVT-601-3101 and 66% vs. 42.6% [p < 0.0001] in MVT-601-3102).

In study MVT-601-3101, all seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, and impact of pain on daily activities as measured by the Endometriosis Health Profile-30 (EHP-30) pain domain, greater proportions of women not using analgesics (p-values < 0.0001), changes in mean nonmenstrual pelvic pain (p = 0.0002), greater proportions of women not using opioids (p = 0.0005), and changes in mean dyspareunia (painful intercourse; p = 0.0149). In study MVT-601-3102, six of seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, impact of pain on daily activities as measured by the EHP-30 pain domain, a greater proportion of women not using opioids (all p-values < 0.0001), changes in nonmenstrual pelvic pain (p = 0.0012), and dyspareunia (painful intercourse; p = 0.0371). Relugolix combination therapy was generally well tolerated with minimal BMD loss over 24 weeks.

In addition, an ovulation inhibition study with relugolix combination therapy in healthy adult premenopausal women has been completed (MVT-601-046, N = 67). This open-label, single-arm study included a pre-treatment period to confirm ovulatory status, an 84-day treatment period to assess the effects of relugolix combination therapy on ovarian activity, and a post-treatment follow-up period to determine time to return of ovulation. Ovulation (as assessed by the Hoogland-Skouby scale [Hoogland and Skouby 1993]) was inhibited for 100% of participants during the entire 84-day treatment period, and ovarian activity, as evidenced by the degree of follicular growth, was markedly suppressed. Pituitary secretion of FSH and LH, and ovarian production of estradiol and progesterone were markedly suppressed with relugolix combination therapy, with median E2 serum concentrations consistently maintained within an approximate range of 30 to 40 pg/mL during the 84-day treatment period. Mean progesterone concentrations were consistently maintained between 0.94 and 1.25 nmol/L, with individual values all below 5 nmol/L, the cut-off value for luteal activity in the Hoogland-Skouby assessment scale, consistent with the suppression of ovulation observed across all three treatment periods. Additionally, endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness consistently maintained between 4 and 5 mm and likely contributing to the reduction in overall bleeding. All women returned to ovulation or began menses upon discontinuation of relugolix combination therapy demonstrating the revisability of the treatment effect. The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days, with 97.01% (65 of 67 participants) having a confirmed ovulation within 36 days post treatment (one participant ovulated on Day 43 and the other began menstruation on Day 39).

As of June 2021, the relugolix clinical development program includes data from 4463 participants and patients exposed to relugolix either as monotherapy or as relugolix combination therapy, and includes 2554 patients exposed for at least 6 months and 1545 patients exposed for at least one year. These data include single doses up to 360 mg and multiple doses up to 120 mg administered for more than a year. Data from the pivotal phase 3 studies in the uterine fibroid indication demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. Data from the pivotal phase 3 studies in the endometriosis indication also demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo.

These collective data continue to support a favorable benefit/risk profile for the proposed indications.

In summary, data from the relugolix nonclinical, pharmacodynamic, and clinical development program support the proposed mechanism of action for relugolix combination therapy, which works through inhibition of follicular development and prevention of ovulation, suppressing the secretion of endogenous estradiol and progesterone. Data from the completed pivotal phase 3 studies demonstrate robust efficacy results for the indications studied. Data from the ovulation inhibition study demonstrate maximal suppression of ovulation. The currently available safety database is large and allows characterization of the safety profiles of relugolix monotherapy and relugolix combination therapy to support initiation of this study. A detailed description of the chemistry, pharmacology, efficacy, and safety of relugolix is provided in the investigator brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of relugolix combination therapy may be found in the current investigator brochure.

2.3.1. Risk Assessment

On the basis of nonclinical studies, clinical safety analyses, and data available for investigations of similar compounds, relugolix combination therapy may be associated with potential risks. The risk assessment and mitigation strategies for this protocol are outlined in Table 2.

Table 2: Study MVT-601-050: Risk Assessment and Mitigation Strategies

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Identified Risk		
Uterine fibroid prolapse or expulsion.	Exclusion of participants with abnormal bleeding due to uterine fibroids or known submucosal uterine fibroids.	Active monitoring of adverse events.
Potential Risk		
Decreased Bone Mineral Density 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.	Exclusion criteria for: – History of osteoporosis, history of treatment for low BMD, current osteoporosis, or low BMD (Z-score $\leq$ -2.0 at lumbar spine, total hip, or femoral neck during the screening period), – History of or current metabolic bone disease, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, 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 BMD eligibility criteria for the study are allowed	Bone mineral density will be monitored at the Baseline, 6-Month, and 12-Month/Early Termination visits with specified discontinuation criteria. There will then be a post-treatment follow-up period with BMD measured again at 6- and 12- months after treatment (PTFU DXA Month 6 and Month 12). Active monitoring of fractures and bone health will be performed. All fractures should be reported within 24 hours of study personnel awareness.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Hepatic Transaminase Elevation Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver biochemical tests (ALT and or AST ≥ 3 x ULN) are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 × ULN; total bilirubin values > 1.5 × ULN.	Hepatic transaminases are monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009) in all relugolix studies. Abnormal liver tests (AST or ALT ≥ 3 × ULN) that develop during the treatment period will be reported within 24 hours of study personnel awareness.
Embolic and Thrombotic Events Oral contraceptives and hormone replacement therapy are associated with an increased risk for a venous or arterial thromboembolic event.	Exclusion of participants with previous or current venous thromboembolism.	Active monitoring of adverse events.
Embryofetal Toxicity In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures similar to those at the recommended human dose. No effects on embryofetal development were observed in rats in a similar study. In both rabbits and rats, no fetal malformations were present at any dose level tested that were associated with relugolix exposures similar to and approximately 733-times the exposures in women at the recommended human dose, respectively. Based on these findings, exposure to relugolix combination therapy early in the first trimester of pregnancy has the potential to increase the risk of early pregnancy loss.	Exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Tumors (Breast and Liver) Breast cancer is a hormonally sensitive tumor. There is substantial evidence that combined oral contraceptives do not increase the incidence of breast cancer. Although past studies have suggested that combined oral contraceptives might increase the incidence of breast cancer, more recent studies have not confirmed such findings. Hepatic adenomas are associated with hormonal contraceptive use and a long-term increased risk of developing hepatocellular carcinoma.	Exclusion criteria for participants with known, suspected, or a history of breast cancer or active liver disease. Exclusion of participants with BRCA mutations or other mutations associated with an increased risk of breast cancer.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase. Mammograms at screening and end-of-treatment for women who are ≥ 40 or who turn 40 during the trial. Active monitoring of adverse events.
Mood Disorders Depression has been reported with the prescribed use of GnRH receptor antagonists and agonists and with combined oral contraceptives and hormone replacement therapy.	Exclusion of participants whose mood disorder has been unstable or not well controlled. Exclusion of participants who have major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria. Exclusion of participants with history of suicidal ideation or suicidal behavior.	Screening for suicidality at baseline using a validated scale. Assessment of mood symptoms at each in-person visit using a validated scale. Active monitoring of adverse events.
Gallbladder Disease Combined hormonal therapy use may be associated with gallbladder disease.	Exclusion criteria for ALT and AST > 2 × ULN; total bilirubin values > 1.5 × ULN.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase and adverse events is performed during the treatment period.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FDA = Food and Drug Administration; GnRH = gonadotropin-releasing hormone; PTFU = post-treatment follow-up; ULN = upper limit of normal.

Adverse drug reactions associated with relugolix combination therapy in women with uterine fibroids include the nonserious adverse events of hot flush, abdominal pain, uterine bleeding, alopecia, libido decreased, irritability, hyperhidrosis, dyspepsia, and breast cyst and serious adverse events of uterine myoma prolapse and expulsion. Adverse drug reactions associated with relugolix combination therapy in women with endometriosis include the nonserious events of headache, hot flush, hyperhidrosis, back pain, arthralgia, libido decreased, metrorrhagia, and vulvovaginal dryness.

In completed phase 1, 2, and 3 studies, there were no drug-specific trends observed in mean or individual patient vital sign measurements, laboratory test results, or electrocardiogram parameters, with the exception of infrequent transient and predominantly mild hepatic transaminase elevations that were observed at a frequency comparable to that in placebo.

No new safety concerns have been identified during active ongoing monitoring.

Overall, the benefit/risk profile remains favorable for the continued development of relugolix combination therapy.

2.3.2. Benefit Assessment

Relugolix combination therapy is a once daily oral medication that has been shown to achieve 100% suppression of ovulation in an ovulation inhibition study (MVT-601-046), suggesting that with appropriate use it has the potential to be a highly effective contraceptive method. Additionally, prompt resumption of ovulation following discontinuation of relugolix combination therapy was observed, indicating the return to fertility is rapid and predictable.

The contraceptive action of relugolix combination therapy is mediated by relugolix, which suppresses follicular development and endogenous production of estrogen and progesterone. The risks of bone loss and vasomotor symptoms associated with a hypoestrogenic state, as well as endometrial hyperplasia from unopposed estrogen, are mitigated by administering relugolix in combination with E2 and NETA at low doses commonly used for hormone replacement therapy in menopause rather than the higher doses used in combined hormonal contraceptives to suppress ovulation. The low dosing of E2 and NETA in relugolix combination therapy may be considered an advantage to those who prefer to minimize the use of exogenous hormones.

Similar to continuous or extended cycle oral contraceptive regimens, relugolix combination therapy may benefit women who wish to limit cyclic bleeding for personal reasons. In the uterine fibroid studies, relugolix combination therapy was associated with an 84.3% reduction in menstrual blood loss volume and a high proportion of patients achieved amenorrhea (52.3% in MVT-601-3001 and 50.4% in MVT-601-3002). This change in the menstrual bleeding pattern may be considered as an advantage to some women.

Relugolix combination therapy has been generally well tolerated in most patients and participants, with an overall low rate of discontinuation due to adverse events.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with relugolix combination therapy are justified by the

anticipated benefits that may be afforded to participants in this study who seek effective contraception.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 3.

Table 3: Study MVT-601-050 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in women with uterine fibroids or endometriosis who are18 to 50 years of age and at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.

Objectives	Endpoints
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To evaluate change in bone mineral density during treatment with relugolix combination therapy.	• Percent change in bone mineral density from baseline to 6 and 12 months on-treatment at lumbar spine (L1-L4), total hip, and femoral neck.
• To evaluate post-treatment change in bone mineral density.	• Percent change from baseline and 12 months on-treatment (or Early Termination) to the 6-month and 12-month post-treatment time points at lumbar spine (L1-L4), total hip, and femoral neck.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

4. STUDY DESIGN

4.1. Overall Design

This is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy. Approximately 1020 sexually active women with uterine fibroids or endometriosis who are 18 to 50 years of age and will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

After participants sign the informed consent form (ICF), their eligibility will be assessed at Screening/Visit 1 (see Schedule of Activities; Table 1). A history of either uterine fibroids and heavy menstrual bleeding or endometriosis with moderate to severe pain will be confirmed.

A participant will be considered to have a history of fibroids if there is documentation of an ultrasound from the last two years showing one or more fibroids and the patient reports heavy menstrual bleeding affecting quality of life. If documentation of an ultrasound cannot be obtained, then an ultrasound may be performed locally to confirm the presence of one or more fibroids. Participants with fibroids will be asked a single question about their menstrual flow to determine eligibility (see Section 8.1.2).

Participants entering with a diagnosis of endometriosis-associated pain must have documentation of directly visualized endometriosis (either on laparoscopy or laparotomy) or histologically-confirmed endometriosis. They will be asked two questions at enrollment to determine eligibility (see Section 8.1.2).

After a thorough review of the participant's medical history, gynecological history including contraception, and use of prior medications, their height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Screening for suicidal ideation and suicidal behavior will be performed using the Columbia Suicide Severity Rating Scale (C-SSRS). See Appendix 8 for a copy of this questionnaire. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy. Participants who are 40 years of age or older at the time of enrollment will need to undergo a screening mammogram locally (see Section 8.2.7. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial), if no normal result is available from an examination within 18 months prior to screening. Screening tests for the sexually transmitted diseases (STD) gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible for rescreening once they have received adequate treatment for the identified STD (see Section 8.1.2). Participants who are noted to have vitamin D deficiency (12-19 ng/mL) may be supplemented with calcium and vitamin D at the discretion of the treating clinician. Participants who fail screening due to vitamin D levels < 12 ng/mL may begin supplementing and subsequently be rescreened at the discretion of the treating clinician. Participants who are supplementing with vitamin D based on low screening vitamin D level or are re-screened after vitamin D supplementation and subsequently enrolled should then have a vitamin D level drawn at Visit 3 (see Table 1). The treating clinician can manage further supplementation based on this repeat level.

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 1b, which will consist of a BMD assessment via dual-energy X-ray absorptiometry (DXA) scan, which should be done between 30 and 15 days prior to Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies.

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. Depression screening (using the Patient Health Questionnaire-9 [PHQ-9]) will be completed. Any patient who scores a 1+ on the question of being bothered in the last two weeks by "Thoughts that you would be better off dead, or of hurting yourself in some way," will need to be further assessed for suicidality using the C-SSRS. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. Home pregnancy tests will be provided for assessment prior to each cycle as required by the study and as needed during the cycle.

If Visit 2 occurs on Days 1-3 of the menstrual cycle for participants not using any contraceptive method or using barrier contraception, or within the appropriate window for participants transitioning from another contraceptive method, the participant will begin her first treatment cycle of relugolix combination therapy by dosing with study medication at Visit 2. If the visit is

not within the window to begin dosing, the participant will be dispensed the study intervention for initiation at home. When the participant reports the onset of the next menses in the eDiary or reaches the appropriate window to begin dosing if transitioning from another contraceptive method, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention. The first dose of study intervention will be confirmed by a phone visit. Once dosing of study intervention begins, the eDiary is organized by 28-day treatment cycles (ie, Cycle 1, 2, 3….), which are successive periods of 28 consecutive days. The eDiary continues with daily questions related to the intake of study intervention and the presence or absence of vaginal bleeding or spotting. At the end of each 28-day treatment cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding treatment cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding treatment cycle. Each subsequent treatment cycle starts with the result of a home pregnancy test, which must be negative and must be entered in the eDiary for a participant to continue in the study.

Participants will return to the clinic in the first week after completion of Cycle 1 for Visit 3. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Other records in the eDiary will be assessed, including use of other forms of contraception, occurrence of sexual intercourse during the first cycle (recorded once, at the end of the cycle), results of home pregnancy tests (if applicable), and the result of the protocol-required home pregnancy test prior to the start of Cycle 2. The occurrence of adverse events and use of concomitant medication since the last visit will be assessed. Body weight and vital signs will be measured. Mood and depression will be assessed using the PHQ-9. Patients who report an answer of 1+ to the question of being bothered in the last two weeks of “Thoughts that you would be better off dead, or of hurting yourself in some way” will need to be further assessed at that visit with the C-SSRS. Blood tests will be obtained. A vitamin D level should be obtained if the treating clinician started supplementation based on vitamin D deficiency. Further supplementation following a normal repeat level will be left up to the discretion of the treating clinician. Study medication will be dispensed. Approximately 6 weeks after Visit 3, a telephone contact will be made (Phone 3; see Table 1), focusing on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable.

On-treatment site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur in the first week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Approximately 6 weeks following each on treatment site visit, the participant will be contacted by telephone (Phone 4, Phone 5, and Phone 6). The site visits will have the same assessments described for Visit 3 above. The telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last on-treatment visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

On-treatment DXA scans are to be completed at 6 and 12 months (± 30 days). The 12-month on-treatment scan should be done as close to 12 months as possible, but may be completed up to the time of Visit 7.

Fourteen days after completion of Cycle 13, or after early discontinuation of treatment, participants will return to the clinic for the follow-up/end-of-treatment (EOT) visit (Visit 7). All assessments done at on-treatment visits will be repeated. In addition, physical, gynecological, and breast examinations will be conducted, and blood samples will be obtained for lab tests along with serum β-hCG to determine pregnancy. A mammogram will be performed, if indicated. Post-treatment contraception will be discussed and any remaining study medication and the eDiary will be collected.

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention (ie, the safety reporting period).

Any participant who has an on-treatment pregnancy or is pregnant at the follow-up/EOT visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Two post-treatment follow-up (PTFU) DXAs will be performed at 6 months and 12 months (PTFU Month 6 and PTFU Month 12), with a limited set of serum labs (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphate) if BMD loss meets prespecified criteria of > 3% loss at any anatomic site or a participant has a Z-score of≤ -2.0. Patients will be contacted at the time of these DXA assessments to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events.

4.2. Scientific Rationale for Study Design

This is an open-label, single-arm, phase 3 study designed to demonstrate the contraceptive efficacy of relugolix combination therapy in the intended treatment population. The primary objective is to assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and are at risk for pregnancy, as expressed by the At-Risk PI in the restricted intent-to-treat (rITT) population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse. Study intervention will be self-administered during 13 consecutive 28-day treatment courses (“cycles”) for a total duration of 52 weeks.

To demonstrate the intrinsic contraceptive efficacy of relugolix combination therapy, a study population of women with uterine fibroids or endometriosis without known impaired fertility is considered adequate if patients have regular menstrual cycles (ie, presumed regular ovulation). To support a proper assessment, women participating in this study should be sexually active with men and should agree to abstain from using other forms of contraception during the treatment period.

Participants will visit the study site approximately every 12 weeks for safety evaluations, which include review of adverse events, eDiary, and concomitant medications, and collection of weight, vital signs (blood pressure, heart rate), and urine pregnancy test. Clinical laboratory evaluations will occur at Visits 1, 3, 4, 5, 6 and 7. The study eligibility criteria were designed to minimize

risk to participants and rules for evaluation of liver test abnormalities, consistent with FDA guidance (FDA 2009), have been incorporated into the protocol.

4.3. Justification for Dose

The relugolix combination therapy doses of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg were selected for this study as they are the proposed clinical doses in women with heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

In replicate pivotal phase 3 trials, within each of the indications studied, a 40-mg dose of relugolix combined with E2 1 mg and NETA 0.5 mg resulted in marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women and a decrease in pelvic pain associated with endometriosis, respectively. Across the development programs, the combination of relugolix with E2 and NETA at the selected doses demonstrated maintenance of BMD and prevented vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen. Across all studies, relugolix combination therapy was generally well tolerated in most participants, with an overall low rate of discontinuation due to adverse events. On the basis of the favorable benefit-risk profile observed in each indication, Myovant intends to commercialize relugolix combination therapy for the treatment of heavy menstrual bleeding associated with uterine fibroids and for pain associated with endometriosis.

In a study evaluating the effects of relugolix combination therapy on ovarian activity in healthy premenopausal women (MVT-601-046), relugolix combination therapy demonstrated inhibition of ovulation, as determined by Hoogland-Skouby score, in 100% of women receiving relugolix combination therapy during the entire 84-day treatment period. Therefore, these same doses are expected to be effective in preventing pregnancy.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed thirteen 28-day treatment cycles, the safety follow-up/ EOT visit (Visit 7), and the PTFU Month 6 and Month 12 DXAs (refer to Schedule of Activities, Table 1).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 50 years of age (inclusive);

3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a diagnosis of uterine fibroids or endometriosis meeting *either* of the below criteria:
    a. Diagnosis of uterine fibroids by confirmation of ultrasound performed in the last 2 years (submucosal fibroids > 50% intracavitary are excluded) and patient report of heavy menstrual bleeding affecting quality of life.

       Note: If an ultrasound report from the last 2 years cannot be located, the participant should undergo transvaginal ultrasound at the time of screening to confirm the presence of one or more uterine fibroids.
    b. Diagnosis of endometriosis and has had, prior to signing the informed consent form, surgical or direct visualization (laparoscopy or laparotomy) and/or histopathologic confirmation of endometriosis, and during the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and/or during nonmenstrual portion of the cycle in the prior month;
6. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
7. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through end of treatment;
8. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
9. Has body mass index (BMI) ≥ 18 kg/m2;
10. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

5.2. Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:
    a. Vascular disease (eg, cerebrovascular disease, coronary artery disease, peripheral vascular disease);

b. Women over 35 who smoke;

c. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation);

d. Inherited or acquired hypercoagulopathies, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant);

Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

   Note: The specific reasons for exclusion should be documented in the interactive web-response system (IWRS).

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Malabsorptive disease (including, but not limited to, inflammatory bowel disease and gastric bypass surgery);
11. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past

year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

12. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
13. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

14. Has a known history of infertility or subfertility (examples include but are not limited to prior ectopic pregnancy, prior surgery of fallopian tube, prior imaging or procedure suggesting non-patent fallopian tube, history of infertility workup or treatments);
15. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
16. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.
17. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, intermenstrual/bleeding between menstrual periods, bleeding from a cervical polyp, recurrent bleeding after intercourse);
18. Has a known submucosal fibroid (> 50% intracavitary);

19. Women with a diagnosis of endometriosis who have had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis.

Other Conditions/Disorders

20. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
21. Has known HIV infection or high risk of contracting human immunodeficiency virus (HIV) (eg, has multiple sexual partners, intravenous drug use in participant or partner);
22. Has a history of malignancy ≤ 5 years prior to signing the ICF, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
23. Has known BRCA mutation or other mutation associated with increased risk of breast cancer;
24. 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;
25. History of suicidal ideation or behavior, or confirmed "yes" to any question (with exception of non-suicidal self-injurious behavior, unless deemed as an unacceptable risk by the investigator) on the C-SSRS;
26. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders (based on Diagnostic and Statistical Manual of Mental Disorders 5 [DSM-5] criteria) who have been unstable or not well controlled based on the investigator or mental health professional's judgement, 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 treatment period should not be enrolled;
27. Has a hepatic hemangioma, or has a history of cholestasis with prior estrogen use or during pregnancy;
28. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
29. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
30. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

31. Has a known or suspected pregnancy;
32. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
33. Is breastfeeding or has breastfed in the last year.

At risk of bone loss or unable to be monitored for changes in bone density

34. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
35. Has a bone mineral density Z-score ≤ -2.0 at lumbar spine, femoral neck, or total hip during the screening period;
36. Screening 25-OH-Vitamin D level < 12 ng/mL (patients with vitamin D deficiency with levels 12-19 ng/mL are permitted if supplementing with vitamin D).

    Note: If patients fail screening because of vitamin D levels, they may begin supplementing with vitamin D at the discretion of the treating clinician and be re-screened eight weeks later.
37. Has a history of or currently has osteoporosis, or other metabolic bone disease, collagen vascular disease, chronic kidney disease (CKD) stage 3 or greater with glomerular filtration rate (GFR) < 60 mL/min/m^2 using Modification of Diet in Renal Disease (MDRD) method, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, hyperthyroidism, anorexia nervosa, abnormal bone mineral metabolism (eg, hypophosphatemia), or low traumatic (fragility) fracture. 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;
38. Past history of use or current use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
39. Prior use of depo-medroxyprogesterone acetate for a treatment period > 2 years.

Concomitant and Recent Medications/Devices

40. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
41. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
42. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein);
43. Has used chronic glucocorticoids that are oral, parenteral, inhaled (prednisone equivalents of ≥ 2.5mg daily for ≥ 3 months) in 12 months prior to the study. Women with epidural or spinal glucocorticoid use at any dose in the last 12 months are excluded.

Miscellaneous

44. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

5.3. Lifestyle Considerations

No restrictions are required for treatment with relugolix combination therapy.

5.4. Screen Failures

Participants who consent to participate in the clinical study but are not subsequently entered in the study are considered to have had a screen failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any serious adverse event.

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Note: the study intervention in this study is relugolix combination therapy, also referred to as either relugolix combination therapy, study medication, or study drug.

6.1. Study Intervention(s) Administered

Fixed-dose combination (FDC) tablets, each consisting of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg will be supplied as immediate-release, yellow, film-coated tablets. In addition to the three active pharmaceutical ingredients, the core tablet formulation consists of compendial grade excipients including mannitol, lactose monohydrate, sodium starch glycolate, hydroxypropyl cellulose, and magnesium stearate.

The study intervention is presented in Table 4.

Table 4: Study MVT-601-050 Study Intervention

Intervention Name	**Relugolix Combination Therapy**
Type	Drug
Dose Formulation	Round film-coated yellow tablet
Unit Dose Strength	FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg)
Dosage Level(s)	Single FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg) QD
Route of Administration	Oral
Use	Experimental

IMP/NIMP	IMP
Sourcing	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee
Packaging and Labeling	Study intervention will be provided in a bottle or blister package. Each will be labeled as required per US requirements.

Abbreviations: E2 = estradiol; FDC= fixed-dose combination; IMP = investigational medicinal product; NETA = norethindrone acetate; NIMP = non-investigational medicinal product; QD = once daily; US = United States.

6.2. Preparation/Handling/Storage/Accountability

Relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablets are supplied to the study site in a bottle or blister cards with 28 tablets. The FDC tablets should be stored in the original closed bottle or blister card.

All study participants will take study intervention comprising one tablet daily at approximately the same time.

If a dose is missed, instructions are as follows:

- If a dose is missed and the error is recognized on the same calendar day, the study intervention should be taken as soon as possible, and then regular dosing should be resumed the next calendar day at the usual time.
- If the missed dose is not recognized until the next calendar day (one missed dose), the dose intended for that calendar day should be taken as soon as possible, and regular dosing should be resumed the following day at the usual time.
- If 2 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time.
- If 3 to 6 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time. Back-up contraception should be used for 7 days.
- If 7 or more consecutive days are missed, the participant should begin using back-up contraception immediately and should be seen for an unscheduled visit. The medical monitor should be contacted.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. Although participants and investigators are not blinded to the study treatment or the study outcome (pregnancy), bias is limited because the diagnosis of pregnancy is an objective measure.

6.4. Study Intervention Compliance

Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles"), for a total duration of 52 weeks (364 days). Participants should complete their eDiary each day on study and should bring all remaining study intervention and all used study intervention packages to each study visit. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for dose interruptions will also be recorded in the eCRF.

6.5. Concomitant Therapy

Concomitant or prior therapies must be recorded including:

- Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements) from signing the ICF through the end of the study; or
- Any vaccine, immunization, or hormonal contraceptive method from 6 months prior to signing the ICF through the end of the study;

This information must be recorded in the following ways:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Medications

Table 5 provides examples of prohibited drug categories and windows of exclusion prior to screening; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding participant use of a particular drug or drug class.

Table 5: Study MVT-601-050 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class and Effect	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zoledronic acid	Any past use is exclusionary.
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Any past use is exclusionary. Calcium and vitamin D2 and vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	3 months Note: All other anticonvulsants are allowed.

Drug Class and Effect	Examples	Window/Comments
P-glycoprotein inhibitors and/or moderate or strong CYP3A inhibitors	amiodarone azithromycin[a] carvedilol[d] clarithromycin[a] cobicistat cyclosporine[b] dronedarone erythromycin[a] gentamicin glecaprevir/pibrentasvir indinavir itraconazole ketoconazole lapatinib propafenone quinidine ranolazine ritonavir sofosbuvir/velpatasvir/ voxilaprevir tetracycline verapamil[c] vemurafenib	14 days or 5 times the elimination half-life, whichever is longer (6 months for amiodarone) For participants requiring a short course of these drugs during the treatment period, investigator must contact the medical monitor for approval and guidance on study intervention administration during this period.
Combined p-glycoprotein and strong CYP3A inducers	carbamazepine lumacaftor mitotane phenobarbital phenytoin rifampin rifapentine St. John's wort	28 days

Drug Class and Effect	Examples	Window/Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of greater than or equal to 2.5 mg every day during the study. Note: Spinal or epidural glucocorticoids are prohibited at any dose. Topical, 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. Washout period 12 months
Hormonal contraceptive pills, patches, and vaginal rings	combined or progestin-only Nuva Ring®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3.
Long-acting injectable hormonal contraceptives	depot medroxyprogesterone acetate	Prior use > 2 years is exclusionary. If use is < 2 years, washout period is 24 months.
Progestin implants and intrauterine devices	Nexplanon® Mirena® Paragard®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3.
GnRH antagonists/agonists	leuprolide acetate injection, such as leuprorelin or goserelin acetate injections elagolix	3 months (6 months for 3-month injections)
Anti-androgens	danazol	4 months
Aromatase inhibitors	anastrozole letrozole	4 months

Drug Class and Effect	Examples	Window/Comments
Progestins	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Selective estrogen receptor modulators	raloxifene bazedoxifene asofoxifene clomifene tamoxifen	2 months
Selective progesterone receptor modulators	mifepristone ulipristal acetate	6 months
Proton pump inhibitor	omeprazole esomeprazole pantoprazole	3 months
Anti-coagulants/ platelets/fibrinolytics	warfarin heparin low molecular weight heparin clopidogrel tranexamic acid vitamin K preparations Factor Xa inhibitors	3 months
SGLT-2 inhibitors/	ertugliflozin dapagliflozin empagliflozin canagliflozin	3 months
Thiazolidinediones	rosiglitazone pioglitazone	3 months

Abbreviation: GnRH = gonadotropin-releasing hormone.
a. Roxithromycin is allowed.
b. Tacrolimus is allowed.
c. Amlodipine, felodipine, and nifedipine are allowed.
d. Metoprolol and atenolol are permitted.

6.6. Dose Modification

The dose level of relugolix combination therapy cannot be modified because it is administered as a single daily tablet.

Participants 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. Back-up contraception should be advised, as appropriate. Participants may subsequently be re-started on study intervention with the written approval of the sponsor (or designee).

6.7. Intervention After the End of the Study

Not applicable to study MVT-601-050.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Any adverse event that is intolerable to the participant 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 participant if dosing continued;
- If it is discovered after enrollment that a participant failed to meet protocol entry criteria and continued participation would pose an unacceptable risk to their health;
- If the following liver test abnormalities develop, study intervention should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until their laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 × ULN; or
  - ALT or AST > 5 × ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QTc corrected using Fridericia's formula (QTcF) prolongation of more than 500 msec on an electrocardiogram done as part of patient care outside of the study protocol;
- If the patient experiences a fragility fracture, develops a Z-score ≤ -2.0, or experiences > 3% loss of BMD at lumbar spine, total hip, or femoral neck compared with the baseline measurement during study participation. In the event of a DXA demonstrating Z-score ≤ -2.0 or BMD loss >3 %, a second DXA scan will be conducted within 30 days and the two DXA results will be averaged. If the average

after repeat confirms this level of bone loss, these patients will need to discontinue the study medication and should remain in the trial for PTFU DXA assessments (see Section 8.2.6);

- Participants who are, in the opinion of the investigator or medical monitor, grossly noncompliant with the protocol requirements. Gross noncompliance includes < 75% compliance with the study intervention over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive visits) with < 50% of the required number of eDiary entries. Investigators will follow-up with the participant to encourage compliance with study intervention or eDiary prior to discontinuing her from the study;
- If the participant becomes pregnant at any time after signing the ICF, she must be withdrawn immediately (see Section 8.3.5 for information on pregnancy reporting);
- Suicidal thoughts or behavior, as confirmed on the C-SSRS (see Section 8.2.8).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. The medical monitor should be consulted in advance of withdrawal whenever possible.

At the time of discontinuing from the study, an EOT visit should be conducted, if possible. See the Schedule of Activities (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed, including post-treatment DXA scans and serum labs.

The participant will be permanently discontinued from the study intervention at that time.

The participant retains the ability to remain in the study for post-treatment bone density follow-up as per protocol.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1). Guidelines to address study conduct related to restrictions arising from the novel coronavirus 2019 global pandemic are addressed in Appendix 9.

8.1. Efficacy Assessments

8.1.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time point as described in the Schedule of Activities (see Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1.2. Screening Period

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, cervical cancer screening) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (see Table 1).

Prior to conducting any screening procedures, participants will be given a full description of the nature and purpose of the study and will be required to provide written informed consent. The investigator or a designated, medically qualified member of the site staff will interview potential participants and establish their eligibility for inclusion. Potential participants will be screened according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively).

The participant's medical history, gynecological history including contraception, and use of prior medications will be reviewed. Menstrual history will be assessed to ensure the participant has a history of regular menstrual cycles every 21 to 35 days when not using hormonal contraception. If the menstrual cycle duration observed during the screening period does not meet eligibility criteria, screening may be extended with approval of the medical monitor.

A history of either uterine fibroids and heavy menstrual bleeding or endometriosis with moderate to severe pain will be confirmed.

A participant will be considered to have a history of fibroids if there is documentation of an ultrasound from the last two years showing one or more fibroids and the patient reports heavy menstrual bleeding affecting quality of life. If documentation of an ultrasound cannot be obtained, then an ultrasound may be performed locally to confirm the presence of one or more fibroids.

At the screening visit, prior to medical review, participants with fibroids will be asked a question about their menstrual flow to determine eligibility. Participants will be allowed to enroll if they answer "yes."

1. **Uterine Fibroid Menstrual Bleeding Severity [UFMBS] (screening)**:Do you have heavy blood flow during your period that makes your quality of life worse?

   No
   Yes

Participants with a diagnosis of endometriosis-associated pain must have documentation of directly visualized endometriosis (either on laparoscopy or laparotomy) or histologically-confirmed endometriosis. They will be asked two questions at enrollment to determine eligibility:

Endometriosis-Associated Pain Severity [EAPS] (screening)
Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button.

1. How would you rate your worst pelvic pain on days you were having your most recent period (meaning, being on your period)?

   Absent
   Mild
   Moderate
   Severe
   Very Severe

2. During the last month, how would you rate your worst pelvic pain on days you were **not** having your period (meaning, **not** on your period)?

   Absent
   Mild
   Moderate
   Severe
   Very Severe

Participants with confirmed endometriosis who answer moderate, severe, or very severe to either question are eligible to participate.

The participant's height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), vitamin D, and β-hCG to rule out pregnancy. A mammogram will be obtained, if indicated. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening tests for the STDs gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible to continue screening once they have received adequate treatment for the identified sexually transmitted disease and if the investigator determines the participant is not at high risk for reinfection (eg, because of multiple sex partners or an untreated partner). Screening for suicidal ideation and behavior will be completed using the C-SSRS. A baseline bone density assessment will be performed via DXA scan 15-30 days prior to the planned Visit 2. If the screening period is extended by more than 6 weeks for any reason, screening laboratories should be repeated prior to administration of the first dose of study medication. In the event that the screening period is extended, every effort should be made to have the patient undergo DXA scan as close to 15-30 days prior to Visit 2 as possible.

8.1.2.1. Rescreening

Participants who fail screening may be rescreened with approval of the medical monitor. Participants who are screen-failed based for vitamin D level < 12ng/mL may be supplemented with vitamin D and calcium at the discretion of the treating clinician and then be re-screened after eight weeks. The option to continue supplementation during the study is left to the discretion of the treating clinician. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

8.1.2.2. 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. Other procedures, including cervical cytology, can be retested once without the permission of the medical monitor if necessary due to technical or logistical issues, such as an inadequate sample. Further retesting or retesting for other reasons requires the approval of the medical monitor.

8.1.3. Treatment Allocation

Participants who meet all eligibility criteria, including history, laboratory test, mammogram if indicated, cervical cytology results, negative screening for suicidal ideation and behavior, and a normal bone density as determined by DXA scan will return for Visit 2, the timing of which depends on contraceptive status at screening. All use of contraceptives must be discontinued prior to Visit 2 (or on the day of Visit 2 if transitioning from an intrauterine device or contraceptive implant).

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine

pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an eDiary, which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. The first dose of study intervention will be administered on site at the time of Visit 2 or at home as described below. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact. Home pregnancy tests will be provided for assessment prior to each 28-day treatment cycle as required by the study and as needed during the cycle.

8.1.3.1. Prior Use of Hormonal Contraception, Implants, or Devices

For participants with prior use of hormonal contraception or implantable devices, the first dose of study intervention will be administered at Visit 2.

If the participant is transitioning from combined hormonal contraceptive pills, patches, or rings, she may schedule Visit 2 on the day she would normally initiate a new contraceptive cycle. If the visit cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

If the participant is transitioning from progestin-only pills she must schedule Visit 2 the day after she takes her last progestin-only pill and use a back-up method for the first 7 days of relugolix combination therapy.

If the participant is transitioning from a contraceptive implant or intrauterine device, she must schedule Visit 2 the day the implant or device is removed and use a back-up method for the first 7 days of relugolix combination therapy. Note that only participants who have requested removal of their implant or intrauterine device for reasons unrelated to the purpose of enrollment may be considered for participation.

Participants with less than two years of use of long-acting injectable contraceptive methods are not eligible to screen for the study until 24 months following their last dose.

8.1.3.2. No Prior Contraceptive Use or Use of Barrier Methods

If the participant was not using any prior contraceptive method or was using barrier contraception (diaphragm, cervical cap, male condom, female condom, or spermicidal foam, sponges, and film), she may schedule Visit 2 on Days 1-3 of the menstrual cycle and the first dose of study intervention will be administered the day of the visit. If the visit cannot be reliably scheduled within the window to begin dosing, the visit should be scheduled prior to the onset of menses. Visit 2 procedures will be conducted, and the participant will begin daily eDiary entries related to the onset of menses. When the participant reports the onset of the next menses in the eDiary, she will be prompted to perform a home urine pregnancy test. With entry of a negative

urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

8.1.4. Treatment Period

Once dosing of study intervention has been initiated, participants will take their study intervention QD. Dosing of study intervention will be organized by "cycles" of successive periods of 28 days. Participants will self-administer study intervention through the completion of Cycle 13. Participants will record compliance with study intervention dosing daily in their eDiary. They will also report information about vaginal bleeding or spotting on a daily basis. At the end of each cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding cycle. Each subsequent cycle starts with the result of a home pregnancy test, which must be negative and entered in the eDiary for the participant to continue the study.

8.1.4.1. Site Visits

Participants will return to the clinic the first week after completion of Cycle 1 for Visit 3.

Subsequent site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur 1 week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Study medication will be dispensed at each visit. See the Schedule of Activities (see Table 1) for assessments required for each visit.

8.1.4.2. Telephone Visits

Approximately 6 weeks following each site visit, the participant will be contacted by telephone (Phone 3, Phone 4, Phone 5, and Phone 6). The first telephone contact will occur approximately 6 weeks after Visit 3. Telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

8.1.4.3. 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 participant'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 (hematology and chemistry), urine or serum pregnancy testing, study intervention compliance, and dispensation of study intervention may be conducted as needed. If the unscheduled visit is related to mood changes, conduct depression and suicidality assessments using the PHQ-9 and C-SSRS as appropriate. Consult with the medical

monitor, if needed, to discuss unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled DXA.

8.1.5. Post-Treatment Period

8.1.5.1. End-of-Treatment Visit

Two weeks after completion of Cycle 13, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on treatment visits will be repeated, and final status assessed; in addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for all labs, as well as serum βhCG to determine pregnancy. A mammogram will be completed, if indicated. A DXA scan will be obtained. Post-treatment follow-up of bone density will be discussed, including time points for post-treatment follow-up DXA at Month 6 and Month 12, and serum labs, if patient meets pre-specified criteria. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

8.1.5.2. Early Termination Visit

If the participant does not complete the study for any reason (including investigator discretion), the reason and circumstances for the participant's early termination must be fully documented. If possible, the assessments specified for the follow-up/EOT visit (Visit 7) should be performed. See Section 8.2.6 for instructions regarding DXA scans associated with early termination. The medical monitor should be consulted in advance of withdrawal whenever possible. Participants who are withdrawn from the study may not be re-enrolled.

8.1.5.3. Pregnancy Visit

If a participant has an on-treatment pregnancy, the site must discontinue the participant from study intervention immediately and have her return for a visit (see Table 1). In addition to the procedures noted in Table 1 (with exception of metabolic bone associated laboratory assessments and DXA) the participant will undergo the following diagnostic procedures:

- Quantitative serum pregnancy test (unless pregnancy already confirmed by transvaginal ultrasound);
- Transvaginal ultrasonography to determine gestational age/estimated date of delivery (EDD).

8.1.6. Efficacy Evaluations

Planned time points for efficacy assessments are provided in the Schedule of Activities (see Table 1).

8.1.6.1. Pregnancy Testing

The contraceptive efficacy of relugolix combination therapy will be evaluated using the number of on-treatment pregnancies. On-treatment pregnancies are pregnancies with an estimated conception date (ECD) between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Pregnancy testing is conducted per the Schedule of Activities (see Table 1) as follows:

- A serum β-hCG pregnancy test is performed at Visit 1 and Visit 7. Serum testing is also performed during the treatment period if an on-treatment pregnancy is suspected or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound). A urine pregnancy test is performed at all site visits after screening and as needed;
- A home urine pregnancy test performed by the participant is required prior to the start of each cycle, and the result must be negative to continue on study. Any on-treatment positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound when applicable).

8.1.6.2. Participant eDiary

All participants enrolled in the study will be provided a device with an application for a participant eDiary at Visit 2, along with detailed instructions for its use. Participants will complete daily eDiary entries including compliance with study intervention dosing and occurrence of vaginal bleeding and its severity (spotting, light, moderate, heavy, and extremely heavy), and monthly assessments of occurrence of sexual intercourse, use of back-up contraception, and home urine pregnancy test results. The eDiary data will be reviewed by the study staff on an ongoing basis and at specified time points as noted in the Schedule of Activities (see Table 1).

8.2. Safety Assessments

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), DXA, mammogram, and clinical laboratory tests. Planned time points for all safety assessments are provided in the Schedule of Activities (see Table 1).

8.2.1. Physical Examinations

A complete physical examination, including gynecological and breast examination, will be conducted at Visit 1 and the follow-up/EOT visit (Visit 7). The examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. Height and weight will also be measured and recorded.

All other physical examinations should focus on signs and symptoms reported by the participant to assess for clinically significant changes from the baseline assessment.

The gynecologic examinations at screening will include testing for gonorrhea and chlamydia. Cervical cytology test must be conducted for participants 21 years or older (or who will become 21 years old during the trial) without an available test result from within 18 months years prior to the Screening Visit and submitted to the central laboratory. A repeat test should be performed for inadequate specimen and submitted to the central laboratory.

A bilateral breast examination will be performed at the time of the gynecologic examination.

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

8.2.2. Vital Signs

Vital signs including heart rate and systolic and diastolic blood pressure will be assessed. Vital signs will be measured with the participant in a seated position and should be preceded by at least 5 minutes of rest with the participant in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

Electrocardiograms are not routinely collected during the study and are to be performed per general clinical safety assessment, as applicable.

8.2.4. Clinical Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Table 1) for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within two weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Table 1).

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, serious adverse event, adverse event, or discontinuation of study intervention), then the results must be recorded in the eCRF**.**

8.2.5. Ultrasound Examinations

Ultrasound examinations are not routinely scheduled throughout this study. In the event that a participant reports a history of fibroids and heavy menstrual bleeding but no documentation of fibroids from the last two years can be obtained, the participant should undergo a transvaginal ultrasound locally to confirm the presence of one or more fibroids.

Ultrasounds will otherwise occur only on an as-needed basis during the study.

8.2.6. 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) at the time points described in the Schedule of Activities (see Table 1). The scans will be read by the central imaging 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 be used at each site and operated in the same scan mode for all scans for an individual patient.

The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study. The following procedures will be followed, per the central imaging laboratory's charter: If all four vertebral levels are not visualized or if a given image set is of insufficient quality to allow proper interpretation, a query will be issued to the investigator to check whether a repeat scan can be performed. If required anatomy is missing from an image and a repeat scan cannot be obtained, it will not be analyzed. Bone density analysis of DXA scans will only be performed when at least 2 evaluable vertebrae are present. In the event that follow-up data are technically inadequate, not compliant with acquisition parameters, unreadable, unable to be re-captured in a timely manner, or electronically/physically missing, the central radiology site will enter "not assessable" into the database.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the baseline, 6- and 12-month on-treatment time points, as well as at 6- and 12-months post-treatment. At the time of these DXA assessments, patients will be asked to confirm medical conditions, surgical conditions, medications, pregnancy status, and fracture events. A limited set of serum labs will be performed if bone mineral density monitoring at any time point demonstrates loss of > 3% compared to pre-treatment baseline or a Z-score of ≤ -2.0. Note that a pregnancy test will need to be completed prior to each DXA.

Participants who develop BMD decline (compared to pre-treatment baseline) of > 3% or a Z-score ≤ -2.0 at any anatomic site (lumbar spine, total hip, or femoral neck) will undergo repeat DXA scan to confirm this measurement within 30 days of the first DXA scan. The two DXA results will be averaged. If the average after repeat confirms this level of bone loss, follow-up of DXA findings will proceed according to the following rules:

- Patients who are on-treatment must be discontinued from study medication and should remain enrolled in the study for post-treatment follow-up bone mineral density monitoring (see Section 7.1). In addition, they should have a limited set of metabolic bone laboratory assessments completed (see Section 1.3) and should be referred to a bone specialist.
- Patients who are in the post-treatment follow-up period should have a limited set of metabolic bone laboratory assessments completed. In addition, they will need to be referred to a bone specialist.

If a patient meets criteria for referral to a bone specialist, the sponsor will provide a report that outlines the background of the study as well as the patient's laboratory and DXA results during the study. This information should be sent to the bone specialist along with the patient referral. The site should send a de-identified summary of the evaluation and management plan to the sponsor once available.

8.2.6.1. Bone Mineral Density Monitoring in the Setting of Early Termination

In the event of early termination due to reasons unrelated to bone density loss, DXA scans should be obtained according to the following rules:

For early termination occurring **prior to completing 6 cycles of study medication**, an early-termination DXA scan is not required. The participant can proceed with PTFU DXA Month 6 and Month 12, along with serum labs if prespecified criteria for bone loss are met.

- For early termination occurring **after completing 6 cycles of study medication**, the patient should complete a DXA at the time of early termination and then PTFU DXA Month 6 and Month 12 and serum labs if prespecified criteria for bone loss are met.

If the 6-month on-treatment DXA was completed within the last 6 weeks and the patient has completed fewer than 8 cycles of study medication, an early termination DXA does not need to be performed and the patient can proceed to PTFU DXA Month 6 and Month 12, along with serum labs, if indicated.

8.2.7. Mammogram

Participants who are ≥ 40 years of age at the time of enrollment will need to undergo a screening mammogram. If a patient turns 40 years old during the trial, she should have a mammogram completed at the end-of-treatment visit. All participants 40 years of age or older at the time of the end of treatment visit will need to undergo a mammogram at that time.

All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 9) and recorded in the eCRF. The following actions will be taken depending on the reading:

- Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;
- Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;
- Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours;
- Patients who have malignant breast lesion(s) or breast carcinoma will not be eligible to participate, per exclusion criteria. If at the end of the study, these patients should be referred to a breast oncologist as soon as possible.

8.2.8. Suicidal Ideation, Depression, and Behavioral Risk Monitoring

All patients will be screened for suicidal ideation and behavior at the screening visit using the C-SSRS. Patients with a confirmed answer of "yes" to any question (with exception of non-suicidal self-injurious behavior) will not be eligible to participate, as per the exclusion criteria. Patients who report non-suicidal self-injurious behavior should not be enrolled if the investigator considers participating in the trial to pose an unacceptable risk.

At each in-person visit after screening (Visits 2-7), patients will undergo depression screening using the PHQ-9. Patients who score ≥ 10 at Visit 2 will need to be further assessed by the investigator for depression and other DSM-5-based diagnoses (per exclusion criterion #26) prior to allocation of study drug. Patients who report an answer of 1+ to the question of being bothered in the last two weeks of "Thoughts that you would be better off dead, or of hurting yourself in some way" should be further assessed with the C-SSRS. If the C-SSRS confirms

suicidal ideation or behavior, the patient must be excluded from trial participation. In the event that a patient reports non-suicidal self-injurious behavior on the C-SSRS, the investigator should assess the event(s), the patient's condition, and the benefits and risks of the patient's continued participation in the study.

Patients with scores ≥ 10 on the PHQ-9 at any time during the study will need to be assessed clinically to determine if they meet criteria for a DSM-5-based diagnosis. If criteria are met for a DSM-5-based diagnosis, the investigator should assess the benefits and risks of the patient continuing participation in the study.

There will be ongoing monitoring of adverse events associated with mood disorders (see also Section 2.3.1).

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency of Collecting Adverse Event and Serious Adverse Event Information

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention (ie, the safety reporting period). 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 intervention.

All serious adverse events will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event after conclusion of the study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse reports are provided in Appendix 3.

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 participant is the preferred method to inquire about adverse event occurrences.

The participant's eDiary entries 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 this instrument, proper follow-up with the participant 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.

8.3.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All serious adverse events and adverse events of clinical interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted. Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will review and then file it along with the investigator brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy Reporting

Details of all pregnancies will be collected after the start of study intervention and until the follow-up visit/EOT (Visit 7) (see Schedule of Activities, Table 1).

If a pregnancy is reported, study intervention should be withdrawn immediately, and the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

8.3.6. Adverse Events of Clinical Interest

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

8.3.6.1. Liver Function Tests ≥ 3 × Upper Limit of Normal

Any ALT or AST elevation of this degree or greater occurring during the safety reporting period (the treatment period through 14 days after the last dose of study intervention) should be reported to the sponsor using the safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. Additional instructions for evaluating participants with an increase in ALT or AST ≥ 3 × ULN may be found in Appendix 5.

8.3.6.1.1. Criteria for Temporary Withholding of Study Intervention 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 intervention should be immediately withheld with appropriate clinical follow-up (including repeat laboratory tests, until the participant's laboratory profile has returned to normal/baseline status), and the event reported per Section 8.3.6 and as a serious adverse event if serious adverse event criteria met, including the underlying diagnosis, as available:

- ALT or AST > 8 × ULN; or
- ALT or AST > 5 × ULN and persists for more than 2 weeks; or
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5; or
- ALT or AST > 3 × 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.

8.3.6.1.2. Criteria for Permanent Discontinuation of Study Intervention in Association with Liver Test Abnormalities

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

1. ALT or AST increases to ≥ 3 × ULN; AND

2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × 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 intervention treatment should be withheld or permanently discontinued as appropriate for the safety of the participant.

8.3.6.2. Bone Fracture Events During the Treatment Period

Bone fractures that occur during the safety reporting period should be reported to the sponsor using the safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. See Appendix 6 for further instructions on reporting.

For fractures that occur during the post-treatment follow-up period, see Section 8.3.8.

8.3.7. Adverse Events Related to Menstrual Bleeding

To ensure consistent reporting, the terms below should be used when participants report alterations from their usual menstrual bleeding pattern that meet adverse event reporting criteria. Select the term that most closely reflects both the volume of the menstrual flow and the frequency/duration/regularity of the bleeding episodes.

- Amenorrhea: Absence of menstrual bleeding
- Spotting Vaginal: Spotting regardless of the frequency/duration/regularity
- Oligomenorrhea: Infrequent bleeding/light or normal volume
- Polymenorrhea: Frequent bleeding/light or normal volume
- Menorrhagia: infrequent or regular frequency bleeding/ heavy volume OR prolonged bleeding regardless of flow volume
- Hypomenorrhea: regular frequency/light volume
- Metrorrhagia: irregular frequency/light or normal volume
- Menometrorrhagia: irregular bleeding/heavy volume

8.3.8. Post-Treatment Follow-Up Period

Treatment-emergent adverse event reporting will complete after the 14-day safety follow-up period. During the post-treatment follow-up period, the sponsor will continue to collect information on events related to bone health, eg, DXA measurements and fracture events. Clinical information for a fracture occurring during the post-treatment follow-up period should be reported using the safety report form within 24 hours of the study site personnel's knowledge of the event even if the event does not meet serious adverse event criteria (see Appendix 6).

8.4. Treatment of Overdose

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

For this study, the protocol-specified dose of relugolix combination therapy is one tablet once daily. 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 participant for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a safety report form according to Appendix 3 whether or not the overdose is associated with an adverse event;
- Document the quantity of the excess dose as well as the duration of the overdosing in the Overdose eCRF page.

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Health Economics/ Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no hypothesis associated with the primary endpoint.

9.2. Sample Size Determination

9.2.1. Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 10,000 menstrual cycles of drug exposure in participants 18 to 50 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of 13 28-day cycles;
- 40% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 5 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

9.2.2. Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% confidence interval (CI) for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$ where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100-woman years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with FDA Guidance for Industry (FDA 2019).

At least 10,000 menstrual cycles of drug exposure will be achieved. Assuming 70% of menstrual cycles are at-risk and 40% dropout rate (assuming discontinuers will on average contribute 5 cycles of exposure), approximately 1020 participants must be enrolled to achieve at

least 7000 at-risk cycles. Additional participants may be enrolled to ensure a minimum of 200 participants completing the study. With 7000 at-risk cycles, the study will have 95% power for the upper limit of the two-sided 95% CI for the Pearl Index to be < 5 in the overall population, assuming that the true Pearl Index is 2 and that a Poisson model is used to achieve the CI.

The study is powered based on the combined patient population of women with uterine fibroids or endometriosis. The study aims to enroll approximately 50% of women with uterine fibroids (with a minimum of 40%) and up to 50% of women with endometriosis(with a minimum of 25%).

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.3. Populations for Analyses

The analysis populations are defined in Table 6.

Table 6: Study MVT-601-050 Analysis Populations

Analysis Population	Description
Enrolled	All participants who have completed the informed consent process, completed screening procedures, and have been allocated to treatment
Intent-to-Treat (ITT)	All participants who receive at least one dose of study intervention
Modified Intent-to-Treat (mITT)	The subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred
Per-Protocol (PP)	The subset of participants in the rITT population with at least one treatment cycle that is also without specific protocol deviations
Restricted Intent-to-Treat (rITT)	The subset of participants included in the ITT population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred

Abbreviations: ICF = informed consent form.

9.4. Statistical Analyses

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be finalized prior to database lock. This section provides a summary of the planned statistical analyses of the endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

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 participants. Categorical data will be summarized by counts and percentages.

The single, final analysis of all efficacy and safety data will occur after approximately 1020 participants have enrolled and been followed for 14 days after cycle 13 or last dose, if not early terminated.

The safety follow-up analysis will occur after participants have completed 12 months post-treatment follow-up, if not early terminated. Safety follow-up analysis will include two post-treatment DXAs to be performed at 6 months and 12 months after the end-of-treatment visit.

9.4.1.1. Handling of Missing Data

At-risk cycles will be considered those cycles in which participants note vaginal intercourse and no birth control methods other than the study drug were used. These two survey questions are asked once in the eDiary at the end of each 28-day cycle. Cycles will not be included as at-risk cycles in the denominator of the PI calculation if the answers to one or both of these survey questions are missing.

If subjects have fewer than 21 days of eDiary entry (< 75% compliance rate) that cycle will not be labeled an at-risk cycle and will not be included as an at-risk cycle in the denominator of the PI calculation.

All cycles in which on-treatment pregnancies occur (regardless of missing eDiary entries or missing survey questions) will be counted as at-risk cycles.

For estimating on-treatment BMD percent change from baseline, to account for any missing BMD assessment at a scheduled visit, a mixed-effects model with repeated measures will be fit to derive the least square means and 95% CI at Month 6 and Month 12. This model will also consider potential confounding effects as covariates such as age at baseline, visit, baseline BMD, race, BMI at baseline, as fixed effects using an unstructured variance-covariance matrix.

Further details on the endpoint analyses including sensitivity analysis, handling of missing data, and statistical methods will be provided in the Statistical Analysis Plan.

9.4.2. Evaluable Cycles and Pearl Index Definitions

Evaluable cycles are defined below and will contribute to the denominator for calculating each type of PI.

- At-Risk PI (primary efficacy endpoint): Cycles without use of any other contraceptive methods and with confirmed vaginal intercourse (At-Risk Cycles).
- Gross PI: On-treatment cycles.
- Modified At-Risk PI: Cycles without use of any other contraceptive methods regardless of occurrence of vaginal intercourse.
- Method Failure PI: At-Risk Cycles without major protocol deviations.

9.4.3. Primary Endpoint

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment:

$$\text{Pearl Index (PI)} = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{number of 28-day at-risk cycles of treatment}}$$

There is no hypothesis associated with the primary endpoint. The primary contraceptive efficacy will be assessed by the point estimate of At-Risk PI and corresponding 95% CI. On-treatment pregnancies are pregnancies with an ECD between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the EDD will be ascertained. The ECD will be calculated as:

$$\text{EDD} - 38 \text{ weeks} = \text{ECD}$$

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses or β-hCG level.

The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse. The numerator and denominator in the At-Risk PI calculation are slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, as the primary contraceptive efficacy analysis, will be conducted using an rITT population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred. The At-Risk PI will be presented together with the two-sided 95% CI calculated based on a Poisson distribution (Benda et al. 2004).

9.4.4. Secondary Endpoints

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution. Specifically:

- The Gross PI will be estimated using the ITT population, defined as participants 18 to 50 years of age at the time of enrollment who have entered the study and have at least one on-treatment cycle.
- The modified PI will be estimated using the modified ITT (mITT) population, defined as the subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred.
- The Method Failure PI will be estimated using the per protocol analysis population, defined as the subset of participants in the rITT population, with at least one treatment cycle that is also without specific protocol deviations. For calculation of

the Method Failure PI, only pregnancies with a conception date during at-risk cycles that were also per protocol are included in the numerator.

- Cumulative 1-year pregnancy rate will be calculated on each of the analysis populations by the Kaplan-Meier (KM) survival analysis. All participants will be followed until they either have an outcome of pregnancy or are censored at the time of their last follow-up. The unit of time in the KM analysis will be the cycle, with pregnancies recorded by cycle of conception. Unlike the PI calculations, cycles based on use of adjunctive contraception will not be excluded.

The primary efficacy endpoint will be assessed by subgroups based on selected baseline characteristics (including age, indication, race, BMI, region, etc.), as appropriate. Details will be included in the Statistical Analysis Plan.

9.4.5. Tertiary/Exploratory Endpoint(s)

Not applicable.

9.4.6. Safety Endpoints

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention treatment, and severity. An adverse event reported more than once for a participant is counted once at the maximum severity or strongest relationship to study intervention treatment when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each 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 bone mineral density lumbar spine (L1-L4), total hip, and femoral neck. The absolute change and percent change from baseline to 6- and 12-month on-treatment time points and associated 95% CIs will be presented for each bone mineral density location. The same analysis will be also performed for the absolute and percent change from baseline to last on-treatment visit (or early termination [ET] visit) to 6- and 12-month post-treatment follow up visits. Additional analyses can be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure, if appropriate.

Bleeding profile, including bleeding intensity and number of bleeding days, will be summarized by descriptive statistics.

9.4.7. Other Analyses

Not applicable.

9.5. Interim Analyses

No formal interim analyses are planned for this study.

9.6. Data Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) 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 DSMB will be outlined in a separate charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/(independent ethics committee) IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosures

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants undergoing rescreening will sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

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

Data Quality Assurance

Documentation Accountability

- All participant data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the completion of the informed consent process by the first participant and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. CLINICAL LABORATORY TESTS

- All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the protocol Schedule of Activities (see Table 1).
- Laboratory requisition forms must be completed, and samples must be clearly labeled with the Participant 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 7.
- Investigators must document their review of each laboratory safety report.
- Local laboratory results are only required in the event that central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7: Study MVT-601-050 Protocol-Required Safety Laboratory Assessments

Chemistry	**Hematology**	**Other**
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Liver tests: Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase LDH	WBC Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Serum Pregnancy Test (β-hCG) Urine Pregnancy Test Hemoglobin A1C International normalized ratio (INR) Thyroid Stimulating Hormone (TSH) Parathyroid hormone (PTH) 25-Hydroxyvitamin D (Vitamin D3)
	Lipid Profile	**Serology**
	Total Cholesterol Low Density Lipoprotein High-Density Lipoprotein Triglycerides	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody Hepatitis D antibody Hepatitis E antibody Epstein-Barr Virus

Abbreviations: β-hCG= beta human chorionic gonadotropin; LDH = lactic acid dehydrogenase; RBC = red blood cells; WBC = white blood cell.

APPENDIX 3. ADVERSE EVENTS DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an adverse event per definition above, then it cannot be a serious adverse event even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient 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 disability/incapacity • 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 with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgement should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include 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.

Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and/or Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event or serious adverse event information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or their representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event or serious adverse event.

Assessment of Intensity

The investigator will make an assessment of intensity for each adverse event and serious adverse event reported during the treatment period and for 14 days after according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). For terms not specified with the CTCAE, the criteria below should be used to determine the grade severity:

Severity 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

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each adverse event.
A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each adverse event, the investigator **must** document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to PHV-Myovant@quintiles.com. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event to PHV-Myovant@quintiles.com.

The investigator may change his/her opinion of causality in light of follow-up information and send a Safety Report Form follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions are to be used for the relationship of the adverse event to study intervention:

- **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.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to PHV-Myovant@quintiles.com within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to IQVIA RDS, Inc. via Paper CRF

- E-mail transmission of the Safety Report Form paper CRF is the preferred method to transmit this information to the global safety database.
- In rare circumstances and in the absence of e-mail or e-fax equipment, notification by telephone is acceptable with a copy of the Safety Report Form data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Safety Report Form within the designated reporting time frames.
- Contacts for serious adverse event reporting follow:

Using a Safety Report Form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study intervention.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Safety Report Form and is as follows:

Site Location	E-mail (Primary Reporting Method)	Fax Number (Secondary Reporting Method)
All Regions	[redacted]	[redacted]

For questions regarding serious adverse event or adverse event of clinical interest reporting, please call:

- North/South America: [redacted]
- Regional toll-free phone and fax lines distributed separately.

The initial report should include:

- Study number (MVT-601-050)
- Site address and number
- Investigator name
- Participant ID number, sex, and age
- Details of study intervention 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 intervention

If the participant 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 intervention 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, stabilization, the event is otherwise explained, or the participant is lost to follow-up. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

APPENDIX 4. COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the pregnancy report form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be a serious adverse event and will be reported as such.
- Any post-study pregnancy related serious adverse event considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female participant who has an on-treatment pregnancy will discontinue study intervention immediately and return for a Pregnancy visit as described in Section 8.1.5.3.

APPENDIX 5. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Study intervention (relugolix combination therapy) should be withheld for any liver test abnormality listed in Section 8.3.6, 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 Table 8, and per the investigations in Table 9. If close monitoring is not possible, study intervention should be withheld even if the results do not meet the criteria for withholding in Section 8.3.6.

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

Table 8: Study MVT-601-050 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (ALT, AST, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If ALT or AST ≥ 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 participant is asymptomatic	Frequency may decrease

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

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

Table 9: Study MVT-601-050 Investigations and 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 Table 8; • 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).

Abbreviations: CBC = complete blood count; INR = International normalized ratio.
Note: If the first follow-up test does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

APPENDIX 6. FRACTURES: INFORMATION FOR REPORTING

Study intervention should be discontinued permanently for any fragility fracture (defined as a fracture occurring as a result of a fall from a standing height or less in the absence of major trauma). The classification of fragility fracture specifically excludes fractures of fingers, toes, face, or skull. Any fracture that occurs during the study should be reported to the sponsor using the designated safety report form.

The following information should be reported to the sponsor:

- Bone(s) that was/were fractured;
- Description of the event leading to the fracture and classification of the fracture as either non-fragility or fragility fracture (see definition above);
- Full assessment of patient's risk factors for fracture and/or confounders for bone loss/fracture;
- Treatment required (none, conservative, surgery, etc.);
- Evidence of healing, if any.

APPENDIX 7. BREAST IMAGING REPORTING AND DATA SYSTEM

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 8. VALIDATED TOOLS FOR DEPRESSION AND SUICIDALITY SCREENING

Scoring of PHQ-9
Note: the PHQ-9 is administered via a paper questionnaire

PHQ-9 Score	Depression Severity	Actions
0-4	None-minimal	If patient answers 1+ on question 9, complete C-SSRS
5-9	Mild	If patient answers 1+ on question 9, complete C-SSRS
10-14	Moderate	Evaluate patient for DSM-5-based diagnoses, consider risks and benefits of continued participation in the study If patient answers 1+ on question 9, complete C-SSRS
15-19	Moderately Severe	Evaluate patient for DSM-5-based diagnoses, consider risks and benefits of continued participation in the study If patient answers 1+ on question 9, complete C-SSRS
20-27	Severe	Evaluate patient for DSM-5-based diagnoses, consider risks and benefits of continued participation in the study If patient answers 1+ on question 9, complete C-SSRS

PHQ-9

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✓" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

(For office coding: Total Score _____ = _____ + _____ +_____)

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
❑	❑	❑	❑

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Columbia Suicide Severity Rating Scale: For Use at Baseline

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain. (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____
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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

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Columbia Suicide Severity Rating Scale: For Use at Visits 2-7 (see Section 8.2.8)

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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APPENDIX 9. GUIDANCE FOR STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The novel coronavirus 2019 (COVID-19) pandemic has impacted the conduct of clinical trials globally. Regional quarantine laws, travel restrictions, and site closures present challenges to normal study conduct and may lead to missed study visits or procedures or an interruption to a patient's study drug supply.

Myovant Sciences has thoroughly reviewed guidance documents from various country and regional regulatory agencies and has put mitigation plans in place to ensure that the safety of patients is maintained, the study continues to be conducted in compliance with Good Clinical Practice (GCP), and risks to the integrity of the study are minimized. These plans will remain in place through the duration of the COVID-19 pandemic.

Safety During the COVID-19 Pandemic

Protecting study patients, investigational site staff and clinical service providers involved in Myovant Sciences clinical studies from activities that may unnecessarily increase the risk of contracting COVID-19 is of utmost importance. Regulations and policies instituted for safety purposes during the COVID-19 pandemic at the institutional, local, country, and regional level should be adhered to.

Protocol Adherence

Wherever possible and safe, study visits and procedures must be performed as outlined in the protocol to ensure patient safety and to maintain the integrity and interpretability of the study data. While modifications to normal study conduct may, in some cases, be necessary and unavoidable, they must be documented and reported where in conflict with the study protocol and this guidance. Deviations from the protocol will be documented, but those resulting specifically from the COVID-19 pandemic will be marked as such. All deviations resulting from the COVID-19 pandemic will be summarized in the clinical study report.

Visit Schedules and Study Procedures

Local policies, institutional restrictions, and/or patient ability/willingness to make site visits may curtail the ability to adhere to the in-person, on-site visit schedule required by the protocol. Investigators at clinical sites should evaluate the appropriateness of an on-site study visit during the COVID-19 pandemic.

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, as close to the visit target date as possible, taking all measures to prevent contracting COVID-19.

- All protocol-required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, Investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.
- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of

the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the Myovant medical monitor for consultation, as necessary.

If the clinical study site is closed or the patient is unable/unwilling to attend on-site study visits due to the COVID-19 pandemic, alternative methods for completing assessments (eg, phone contact or virtual visit) should be implemented.

- Investigators must assess and evaluate the patient's continued participation and dosing with limited safety assessment.
- At a minimum, investigational site staff should make every attempt to contact the patient via telephone when an expected visit is due or missed to assess for adverse events, document concomitant medications, and study drug dosing since the last study visit.
- If the safety blood draws cannot be performed through the central laboratory per protocol, the investigator may advise the patient to have blood drawn at a local laboratory if there is a safety concern. If two consecutive study visits are missed and the patient is unable to return to the site, the investigator should advise the patient to have protocol-specified safety labs completed at a local laboratory to assess for any safety concerns. In both cases, the local laboratory results should be documented in the eCRF.
- Investigational sites should report all serious adverse events, adverse events of clinical interest, overdose, and pregnancy that the patient reports during these calls within 24 hours of awareness.
- Patients should be reminded of the importance of taking study drug daily or of using back-up contraception if study drug is interrupted.
- Study patients should continue to complete their daily eDiary, even if they run out of study drug, and site staff should motivate them to do so.

Patients should have the contact details of the investigational site medical staff to report any medical issues, including adverse events they may experience in real time.

As soon as the study patients are able to return to the investigational site for an on-site visit, they should do so. The next scheduled visit should occur on the target date as per the Schedule of Activities (see Table 1).

Study Participant Study Drug Supply

If a regional lockdown, travel restrictions, or site closure is imminent due to the COVID-19 pandemic, sites are encouraged to dispense additional study drug at an expected study visit or request patients to return for an unscheduled visit for additional study drug dispensation so patients have sufficient supply until their next upcoming visit. Patients should be instructed to contact the site to report any medical issues they may experience and site staff should communicate with the patients to determine if it is appropriate for the patient to continue dosing with study drug if/when in-person study visits are not possible.

For cases where study patients are unable to visit the investigational site to pick up study drug, a direct-to-patient delivery of study drug by site staff or shipment via contracted courier may be possible. Consent authorizing direct-to-patient supply will be obtained. Sites should defer to national guidance on how this will occur. Where permitted by national guidance, verbal consent will be taken via telephone or video call and noted in the patient's source file. Where required, by national guidance, this will be followed up with written consent during the next clinic visit. Every effort will be made to obtain the patient's written consent for direct-to-patient delivery prior to delivery or shipment, where this is required by national guidance.

In the event that none of the above are possible for participants to continue taking study medication, a patient may need to be discontinued per the study protocol. Such decisions will be made on a case-by-case basis in discussion with the investigator and medical monitor.

On-Site Study Monitoring Restrictions

In the event study monitors/clinical research associates are not allowed to travel and/or return to a clinical site to monitor and source document verify study data, Myovant has developed plans to ensure monitors:

- Remotely verify source documentation as much data as reasonably possible without burdening sites, if allowed by the study site and country regulations, focusing on pages key to the interpretability of the study and the safety of participants.
- Remotely monitor study data through cross checking of various systems housing patient data against what is captured in the eCRFs.

Additional guidance on conducting clinical trials during the COVID-19 pandemic may be found in the following documents released by Regional Health Authorities, which may be updated (updates supersede the versions listed here):

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated 27 Jan 2021);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – Version 4 04 Feb 2021.

APPENDIX 10. ABBREVIATIONS

List of Abbreviations and Definition of Terms

Abbreviation	Definition
β-hCG	beta human chorionic gonadotropin
AGC	atypical glandular cell
AGUS	atypical glandular cells of undetermined significance
AIS	adenocarcinoma in situ
ALT	alanine aminotransferase
ASC-H	atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
ATE	arterial thrombotic or thromboembolic event
BMD	bone mineral density
BMI	body mass index
C-SSRS	Columbia Suicide Severity Rating Scale
CI	confidence interval
CKD	chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	novel coronavirus 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
DXA	dual-energy X-ray absorptiometry
E2	estradiol
ECD	estimated conception date
eCRF	electronic case report form
EDD	estimated date of delivery
eDiary	electronic diary
EHP-30	Endometriosis Health Profile-30
EOT	end-of-treatment
ET	early termination
FDA	Food and Drug Administration
FDC	fixed-dose combination (tablet)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone

Abbreviation	Definition
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-response system
KM	Kaplan Meier
LH	luteinizing hormone
LSIL	low-grade squamous intraepithelial lesion
MBL	menstrual blood loss
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified ITT
NETA	norethindrone acetate
PHQ-9	Patient Health Questionnaire-9
PI	Pearl Index
PTFU	post-treatment follow-up
PTH	parathyroid hormone
QD	once daily
QTcF	QTc corrected using Fridericia's formula
rITT	restricted intent-to-treat
STD	sexually transmitted disease
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

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Clinical Study Protocol

Protocol Title:	A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy
Protocol Number:	MVT-601-050
Amendment Number:	2
Compound:	Relugolix Combination Therapy (relugolix, estradiol, norethindrone acetate)
Study Phase:	Phase 3
Short Title:	A Phase 3 Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis who are at Risk for Pregnancy
Sponsor Name:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Agency Identifier Numbers:	IND 131161
Approval Date:	Original: 12 Aug 2020 Amendment 1: 22 Dec 2020 Amendment 2: 07 Jul 2021

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authorization from Myovant Sciences GmbH, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy

Protocol Number: MVT-601-050 Amendment 2

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

[redacted]

07-Jul-2021 | 10:35 AM PDT

Date

07-Jul-2021 | 10:44 AM PDT

Date

07-Jul-2021 | 11:30 AM PDT

Date

07-Jul-2021 | 12:38 PM PDT

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)	Principal Investigator Signature
Clinical Site Number	Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Single-Arm, Open-Label Study to Evaluate the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Uterine Fibroids or Endometriosis Who Are 18 to 50 Years of Age and at Risk for Pregnancy

Short Title: A Phase 3 Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women with Fibroids or Endometriosis Who Are at Risk for Pregnancy

Protocol Number: MVT-601-050

Location: North America

Study Centers: Approximately 100 sites

Study Phase: Phase 3

Target Population: Women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy

Rationale:

This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy. Myovant is developing relugolix combination therapy for the indications of the management of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis. Both conditions are prevalent in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy of relugolix combination therapy in treatment of symptoms associated with endometriosis or uterine fibroids, or the safety of patients undergoing treatment with relugolix combination therapy. By quantifying the contraceptive effectiveness of relugolix combination therapy (using the Pearl Index [PI]), results from this study will provide evidence for patients and their healthcare providers to make an informed decision about the need to use additional nonhormonal contraception while being treated with relugolix combination therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: $PI = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy:	
Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
"Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
"Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
Contraceptive efficacy in various populations and analysis sets.	Cumulative 1-year pregnancy rates.
Safety	
To describe the safety of relugolix combination therapy.	Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
To evaluate change in bone mineral density during treatment with relugolix combination therapy.	Percent change in bone mineral density from baseline to 6 and 12 months on-treatment at lumbar spine (L1-L4), total hip, and femoral neck.

Objectives	Endpoints
To evaluate post-treatment change in bone mineral density.	Percent change from baseline and 12 months on-treatment (or Early Termination) to the 6-month and 12-month post-treatment time points at lumbar spine (L1-L4), total hip, and femoral neck.
To estimate discontinuation rate.	Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

Overall Design:

Study MVT-601-050 is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy (relugolix 40 mg, estradiol [E2] 1 mg, and norethindrone acetate [NETA] 0.5 mg). Approximately 1020 sexually active women with uterine fibroids or endometriosis who are 18 to 50 years of age and will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

The study period consists of a Screening Period (Visit 1), a 52-week Treatment Period (Visits 2 to 6), a 14-day post-treatment Safety Follow-Up Period (Visit 7), as well as a 12-month Post-Treatment Follow-Up (PTFU) period during which bone mineral density (BMD) is monitored.

Participant eligibility will be determined based on assessments performed at Visit 1. The participant's medical and gynecological history (including contraception and use of prior medications) will be reviewed and a diagnosis of either uterine fibroids with heavy menstrual bleeding or endometriosis with associated pain will be confirmed (see inclusion criteria). An ultrasound may be performed to confirm diagnosis of uterine fibroids if there is no previous documented record from the past two years. Height, weight, and vital signs will be measured; and physical, gynecological, and breast examinations will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy, and participants will be screened for the sexually transmitted diseases (STDs) gonorrhea and chlamydia. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Participants who are 40 or older will need to undergo a screening mammogram (see Appendix 7).

Participants who meet all eligibility criteria will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Prior to initiation of treatment with relugolix combination therapy on Day 1 (Visit 2), patients will need to undergo a baseline assessment of bone mineral density via dual-energy X-ray absorptiometry (DXA) scan. On Day 1 (Visit 2), continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. Participants must have a negative urine pregnancy test.

Participants will also receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Finally, study medication will be dispensed, together with instructions for administration and back-up contraception, if applicable. The window for initiating dosing with relugolix combination therapy also depends upon contraceptive status. If Visit 2 occurs within the correct window, dosing may begin at Visit 2. Otherwise, the participant will initiate dosing at home when the appropriate window is reached and after another negative urine pregnancy test result is recorded in the eDiary. Thereafter, continuous treatment with relugolix combination therapy will be taken for 13 consecutive 28-day treatment cycles.

Throughout the Treatment Period, compliance with study intervention administration will be recorded daily in the eDiary. At the completion of each 28-day treatment cycle, the participant will record the results of a urine pregnancy test and indicate whether intercourse or use of additional contraception occurred during the previous 28-day treatment cycle. Each treatment cycle starts with the result of a home pregnancy test, the result of which must be negative and must be entered in the eDiary for a participant to continue in the study. Assessments of safety (physical, gynecological, and breast examinations; laboratory assessments; vital signs, etc.) will be performed throughout the study. DXA scans will be performed at 6-month intervals during treatment and the post-treatment follow-up period. Telephone visits to assess compliance and safety will be performed approximately 6 weeks following each on-site visit during the treatment period.

Fourteen days after discontinuation of treatment, a follow-up/end-of-treatment (EOT) visit (Visit 7) will be conducted. All assessments done at on-treatment visits will be repeated and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for selected serum chemistry assessments, including β-hCG to determine pregnancy and safety assessments will be performed. A 12-month on-treatment DXA will be performed no later than the time of this visit. A mammogram will be performed, if indicated. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

Two PTFU DXAs will be performed at 6 months and 12 months after the end-of-treatment visit. Clinical laboratory tests (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphate) will be performed if bone mineral density loss meets pre-specified criteria. Any participant who has an on-treatment pregnancy will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Inclusion and Exclusion Criteria:

Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 50 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;

4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a diagnosis of uterine fibroids or endometriosis meeting *either* of the below criteria:
    a. Diagnosis of uterine fibroids by confirmation of ultrasound performed in the last 2 years (submucosal fibroids > 50% intracavitary are excluded) and patient report of heavy menstrual bleeding affecting quality of life.

        Note: If an ultrasound report from the last 2 years cannot be located, the participant should undergo transvaginal ultrasound at the time of screening to confirm the presence of one or more uterine fibroids.

    b. Diagnosis of endometriosis and has had, prior to signing the informed consent form, surgical or direct visualization (laparoscopy or laparotomy) and/or histopathologic confirmation of endometriosis, and during the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and/or during non-menstrual portion of the cycle in the prior month;
6. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
7. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through end of treatment;
8. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
9. Has body mass index (BMI) $\geq$ 18 kg/m^2;
10. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

<u>Exclusion Criteria</u>

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:
    a. Vascular disease (eg, cerebrovascular disease, coronary artery disease, peripheral vascular disease);
    b. Women over 35 who smoke;
    c. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation);

d. Inherited or acquired hypercoagulopathies, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant);

Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

   Note: The specific reasons for exclusion should be documented in the interactive web-response system (IWRS).

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Malabsorptive disease (including, but not limited to, inflammatory bowel disease and gastric bypass surgery);
11. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

12. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
    d. High-density lipoprotein level < 50 mg/dL.
13. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

14. Has a known history of infertility or subfertility (examples include but are not limited to prior ectopic pregnancy, prior surgery of fallopian tube, prior imaging or procedure suggesting non-patent fallopian tube, history of infertility workup or treatments);
15. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
16. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.
17. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, intermenstrual/bleeding between menstrual periods, bleeding from a cervical polyp, recurrent bleeding after intercourse);
18. Has a known submucosal fibroid (> 50% intracavitary);
19. Women with a diagnosis of endometriosis who have had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis.

Other Conditions/Disorders

20. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
21. Has known human immunodeficiency virus (HIV) infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
22. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
23. Has known BRCA mutation or other mutation associated with increased risk of breast cancer;
24. 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;
25. History of suicidal ideation or suicidal behavior;
26. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants 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 or mental health professional's judgement, 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 treatment period should not be enrolled;
27. Has a hepatic hemangioma, or has a history of cholestasis with prior estrogen use or during pregnancy;
28. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
29. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
30. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

31. Has a known or suspected pregnancy;
32. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
33. Is breastfeeding or has breastfed in the last year.

At risk of bone loss or unable to be monitored for changes in bone density

34. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
35. Has a bone mineral density Z-score ≤ -2.0 at lumbar spine, femoral neck, or total hip during the screening period;
36. Screening 25-OH-Vitamin D level < 12 ng/mL (patients with vitamin D deficiency with levels 12-19 ng/mL are permitted if supplementing with vitamin D);

    Note: If patients fail screening because of vitamin D levels, they may begin supplementing with vitamin D at the discretion of the treating clinician and be re-screened eight weeks later.
37. Has a history of or currently has osteoporosis, or other metabolic bone disease, collagen vascular disease, chronic kidney disease (CKD) stage 3 or greater with glomerular filtration rate (GFR) < 60 mL/min/m^2 using Modification of Diet in Renal Disease (MDRD) method, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, hyperthyroidism, anorexia nervosa, abnormal bone mineral metabolism (eg, hypophosphatemia), or low traumatic (fragility) fracture. 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;
38. Past history of use or current use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
39. Prior use of depo-medroxyprogesterone acetate for a treatment period > 2 years.

Concomitant and Recent Medications/Devices

40. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
41. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
42. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein);
43. Has used chronic glucocorticoids that are oral, parenteral, inhaled (prednisone equivalents of ≥ 2.5mg daily for ≥ 3 months) in 12 months prior to the study. Women with epidural or spinal glucocorticoid use at any dose in the last 12 months are excluded.

Miscellaneous

44. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

Disclosure Statement

This is a single arm, open-label study to evaluate the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy.

Number of Participants:

Approximately 1020 participants will be enrolled. The sample size has been set to attain at least 10,000 treatment cycles and 7000 at-risk treatment cycles for pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse) in participants 18 to 50 years of age at the time of enrollment (see Section 9.2). Additional participants may be enrolled to ensure a minimum of 200 participants completing the study. The enrollment aim is approximately 50% of participants with uterine fibroids (with a minimum of 40%), and approximately 50% of participants with endometriosis (with a minimum of 25%).

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study but do not participate in the study are not considered enrolled.

Intervention Groups and Duration:

Relugolix combination therapy (relugolix 40 mg, E2 1 mg, and NETA 0.5 mg) as a fixed-dose combination tablet is to be taken orally QD at approximately the same time each day. Relugolix combination therapy treatment is continuous; that is, a tablet is to be taken daily for the entire duration of the treatment period, without a drug-free interval.

Study intervention will be self-administered during 13 consecutive 28-day treatment periods ("Cycles"), for a total duration of 52 weeks.

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

Participants may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove participants from therapy under this protocol for reasons of safety and/or lack of compliance, as discussed below. Participants removed from study intervention for any reason will, if possible, undergo assessments for an early termination visit (see Schedule of Activities, Section 1.3), then return again approximately 14 days after the end of treatment (ie, after the participant's last dose of study intervention). If the patient has provided consent, she will be recommended to undergo PTFU BMD assessments with DXA and collection of blood samples for clinical laboratory tests at 6 and 12 months (if meeting prespecified criteria).

Criteria for Evaluation:

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the estimated date of delivery (EDD) will be ascertained. The estimated conception date (ECD) will be calculated as:

- EDD − 38 weeks = ECD

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses, or β-hCG level.

Statistical Methods:

Contraceptive Efficacy

This study has one primary endpoint, the At-Risk PI, calculated on the basis of the number of on-treatment pregnancies in the numerator and the number of at-risk cycles of exposure in the denominator. The numerator and denominator are thus slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, the primary contraceptive efficacy analysis, will be conducted using a restricted intent-to-treat (rITT) population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred (ie, a treatment cycle containing an ECD for a pregnancy). The At-Risk PI will be presented together with the two-sided 95% confidence interval (CI) calculated based on a Poisson distribution (Benda et al. 2004). There is no hypothesis associated with the primary endpoint.

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution.

Safety

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, laboratory evaluations, mammogram, and DXA scans.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention, and severity. An adverse event reported more than once for a participant will be

counted once at the maximum severity or strongest relationship to study intervention when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Mammograms will be obtained at baseline and then at the end of treatment for women who are age 40 or older.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the baseline, 6- and 12-month on-treatment time points, as well as at 6-and 12-months post-treatment (hereafter referred to as PTFU Month 6 and PTFU Month 12). All patients who discontinue treatment prior to completing 13 cycles of study medication will still undergo PTFU Month 6 and PTFU Month 12 DXA assessments. The percent change in BMD will be measured at all time points relative to the baseline value.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

Sample Size Determination

Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 10,000 treatment cycles in participants 18 to 50 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of thirteen 28-day treatment cycles;
- 40% of participants will discontinue the study;
- Participants who discontinue will, on average, contribute 5 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% CI for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$, where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100 woman-years (or 1300 28-day cycles). Based on this model, a 95% CI

was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with the FDA Guidance for Industry (FDA 2019).

Assuming 70% of menstrual cycles are at-risk and a 40% dropout rate (assuming participants who discontinue will on average contribute 5 cycles of exposure), approximately 1020 participants must be enrolled to achieve at least 7000 at-risk cycles. A minimum of 200 participants completing the study will be ensured. With 7000 at-risk cycles, the study will have 95% power for the upper limit of the two-sided 95% CI for the Pearl Index to be < 5 in the overall population, assuming that the true Pearl Index is 2 and that a Poisson model is used to achieve the CI. Myovant has powered the study based on the combined population of women with uterine fibroids or endometriosis. The study aims to enroll approximately 50% of women with uterine fibroids (with a minimum of 40%) and approximately 50% of women with endometriosis (with a minimum of 25%).

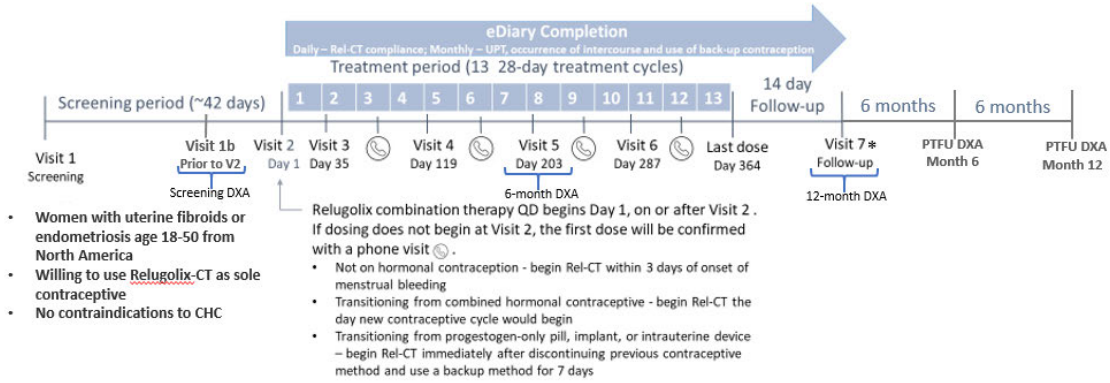
Data Monitoring Committee

An independent Data Monitoring Committee 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 Monitoring Committee will be outlined in a separate charter.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: MVT-601-050 Study Schematic



Abbreviations: CHC = combined hormonal contraceptive; DXA = dual energy X-ray absorptiometry; E2 = estradiol; eDiary = electronic diary; NETA = norethindrone acetate; PTFU = post-treatment follow-up; QD = once daily; Rel-CT = relugolix combination therapy (relugolix 40 mg, E2 1 mg, NETA 0.5 mg); UPT = urine pregnancy test.
* or 14 days after the last dose.
Note: During the treatment period Visits occur approximately 7 days after the end of the previous cycle. Phone visits occur approximately 6 weeks after the subsequent Visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities for MVT-601-050

Trial Period	**Screening**		**Allocation**	**Treatment Period**							
Visit	**V1**	**V1B**	**V2[a]**	**V3**	**P3**	**V4**	**P4**	**V5**	**P5**	**V6**	**P6**
Visit Timing	**−42 D**	**-30D to -15 D**	**On or prior to D1[b]**	**7 days after Cycle 1**	**~6 wks after V3**	**~7 days after Cycle 4**	**~6 wks after V4**	**7 days after Cycle 7**	**~6 wks after V5**	**7 days after Cycle 10**	**~6 wks after V6**
Day of Study Intervention Treatment[c]			**D 1[d]**	**D 35**	**D 77**	**D 119**	**D 161**	**D 203**	**D 245**	**D 287**	**D 329**
Informed Consent	X										
Inclusion/Exclusion Criteria	X		X								
Medical History	X										
Gynecological History	X										
Prior and Concomitant Medication	X		X	X	X	X	X	X	X	X	X
Contraceptive History	X		X								
Dispense eDiary			X								
eDiary Training/Re-Training[e]			X	X	X	X	X	X	X	X	X
Dispense Study Intervention			X	X		X		X		X	
eDiary Compliance/Data Review				X	X	X	X	X	X	X	X
Drug Accountability[f]				X		X		X		X	
Contraceptive Counseling										X[g]	X[g]
Physical Examination[h,i]	X										
GYN & Breast Examination[i]	X										
Height	X										
Weight, Vital Signs (HR, BP)	X		X	X		X		X		X	
Adverse Event Monitoring	X		X	X	X	X	X	X	X	X	X
Clinical Laboratory[j]	X			X		X		X		X	
Gonorrhea/Chlamydia Test	X										
Cervical Cytology[k]	X										
Mammogram[u]	X										
Serum β-hCG[l]	X										
Urine Pregnancy Test[m]			X	X		X		X		X	
Transvaginal ultrasound[v]	X										

Bone densitometry[r]		X[s]			X	X[t]

Table 1: Schedule of Activities for MVT-601-050 (Continued)

Trial Period	**Post-Treatment Period**				
Visit	**Follow-Up/ EOT (V7)[n]/ Early Termination**	**6-months Post-Treatment (PTFU 6-month)**	**12-months Post-treatment (PTFU 12-month)**	**Pregnancy**	**Unscheduled**
Visit Timing	**14 days after Cycle 13 or Last Dose**	**(+/- 30 days)**	**(+/- 30 days)**	**Upon diagnosis**	
Day of Study Intervention	**D378**			**NA**	**NA**
Informed Consent					
Inclusion/Exclusion Criteria					
Medical History					
Gynecological History					
Prior and Concomitant	X			X	X±
Contraceptive History					
Dispense eDiary					
eDiary Training/Re-Training[e]					X[p]
Dispense Study Medication					X[p]
eDiary Compliance/Data	X			X	X[p]
Drug Accountability[f]	X			X	X[p,q]
Contraceptive Counseling	X[g]				
Physical Examination[h,i]	X			X	X[p]
GYN & Breast Examination[i]	X			X	X[p]
Height					X[p]
Weight, Vital Signs (HR, BP)	X			X	X[p]
Adverse Event Monitoring	X			X	X
Clinical Laboratory[j]	X	X	X	X	X[p]
Gonorrhea/Chlamydia Test					X[p]
Cervical Cytology[k]					X[p]
Mammogram[u]	X				
Serum β-hCG[l]	X			X	X[p]
Urine Pregnancy Test[m]	X				X[p]
Transvaginal ultrasound[v]				X[o]	

Bone densitometry[r]	X[t]	X	X		

Abbreviations: β-hCG = beta human chorionic gonadotropin; AGC = atypical glandular cells; AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; ALT = alanine transaminase; ASC-H = atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; AST = aspartate transaminase; BP = blood pressure; D = day(s); EDD = estimated date of delivery; eDiary = electronic diary; EOT = end-of-treatment; GGT = gamma-glutamyl transferase; GYN gynecologic; HPV = human papilloma virus; HR = heart rate; HSIL = high-grade squamous intraepithelial lesion; LDH = lactic dehydrogenase; LSIL = low-grade squamous intraepithelial lesion; NA= not applicable; P = phone contact; V = visit.

a. The timing of Visit 2 depends on contraceptive status at screening and the need for washout. Visit 2 should occur after screening tests results indicating eligibility are available.
b. Study intervention dosing (Day 1) occurs during the allocation period (Visit 2). The timing of Day 1 may vary based on the following:
    - For participants not using any prior contraceptive method or using barrier contraception Day 1 must occur within 3 days of the onset of menses and after a negative urine pregnancy test has been recorded in the participant's eDiary. If Visit 2 occurs within 3 days of the onset of menses, the participant will begin her first treatment cycle of relugolix combination therapy dosing at the study visit. If the visit is not within this window, dosing will begin once the participant reports the onset of the next menses, followed by entry of a negative urine pregnancy test result in the eDiary. The eDiary will then instruct the participant to take and record the first dose of study intervention.
    - For participants transitioning from combined hormonal contraceptive pills, patches, or rings: Day 1 is the day she would normally initiate a new contraceptive cycle. If Visit 2 cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.
    - For participants transitioning from progestin-only pills: Visit 2/Day 1 must be scheduled the day after completing treatment with the prior method and the participant must use a back-up method for the first 7 days of relugolix combination therapy.
    - For participants using a contraceptive implant or intrauterine device: Visit 2/Day 1 must be scheduled the day the implant or device is removed. The participant must use a back-up contraceptive method for the first 7 days of relugolix combination therapy.
c. Visits should be scheduled on the target day of study intervention treatment as indicated. If this this not feasible, the visit should occur as soon after the target day as possible. Treatment must not be extended beyond Day 364.
d. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact.
e. Initial eDiary training to be performed when eDiary is dispensed. eDiary training for the participant should be performed/reinforced throughout the study.
f. The participant should be asked to bring all study intervention to the clinic for each visit (see Section 6.4).
g. Counseling regarding post-trial contraceptive use should be provided to all participants at Visit 6 and repeated at Phone Visit 6 and Visit 7 (Follow-up/EOT).
h. A complete physical exam will be conducted at Visit 1 and Visit 7 and will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All other physical examinations should focus on signs and symptoms reported by the participant.
i. Physical, gynecologic, and breast examinations should be conducted by a licensed health professional (eg, physician, nurse practitioner, physician assistant).
j. Clinical laboratory tests will include hematology, chemistry with phosphate, lipid profile, thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), vitamin D, and hemoglobin A1C at screening (see Appendix 2). The screening sample must be obtained in the fasted state (no food or drink other than water after midnight). If the screening period is extended by more than 6 weeks for any reason, screening laboratories (chemistry and hematology) should be repeated prior to administration of the first dose of study intervention. If vitamin D supplementation was started for vitamin D deficiency in the screening period, a vitamin D level should be drawn at Visit 3. Assessments at Visits 3, 4, and 6 will otherwise only include liver function tests (ALT, AST, GGT,

total bilirubin, alkaline phosphatase, lactate dehydrogenase. Visits 5 and 7 will include hematology, chemistry, serum β-hCG, and lipid profile (perform TSH, PTH, vitamin D if BMD loss ≥ 3% or Z-score ≤ -2.0 at PTFU Month 6 or Month 12 DXA). If labs are obtained due to bone mineral density loss of ≥ 3% or Z-score ≤ -2.0 in the post-treatment follow-up period, labs will be limited to vitamin D, TSH, PTH, creatinine, calcium, and phosphate.

k. Cervical smear is only applicable to participants 21 years of age and older (or who will become age 21 during the course of the trial). Cervical cytology does not need to be performed if a normal cervical smear (ie, no evidence of ASCUS with high-risk HPV positive, ASC-H, LSIL, HSIL, squamous cell carcinoma, AGUS, AGC-neoplastic or AIS) performed within 18 months of Visit 1 can be documented and the participant does not report a history of abnormal results within the past 3 years. Cervical smear may be performed by a nurse practitioner or physician's assistant if licensed in the state, is trained, and it is within their scope of practice.
l. A serum β-hCG pregnancy test is required at Visit 1 and Visit 7 (Follow-up/EOT). Serum testing should also be performed during the trial if a pregnancy is suspected, or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound).
m. A urine pregnancy test will be performed at each site visit after screening and prior to each DXA. Additionally, a home urine pregnancy test performed by the participant is required prior to the start of each cycle and the result must be negative to continue. Any positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound, when applicable).
n. Follow-up/EOT visit also to be done in case of early discontinuation.
o. Transvaginal ultrasonography will be performed to determine gestational age/EDD.
p. For an unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
q. eDiary and any remaining drug should be collected by the site at this visit.
r. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading. A screening, 6- and 12-month on-treatment, and post-treatment follow-up (PTFU) Month 6 and Month 12 DXA will be performed within ± 30 days of the recommended time frame. For further details, see Section 8.2.6.
s. DXA should not be completed before normal baseline physical exam, pathology, laboratory studies, and pregnancy test are completed. The DXA should be performed between 30 to 15 days prior to allocation of investigational product to account for the possibility that a repeat scan will need to be performed.
t. The 12-month on-treatment DXA may occur at the end-of-treatment (EOT) visit. If performing the early termination visit, refer to Section 8.2.6.1 for detailed guidance on whether a DXA needs to be performed.
u. For patients ≥ 40 years old at the time of enrollment and at the post-treatment follow-up visit, if this occurs ≥ 1 year past last mammogram.
v. Patients with uterine fibroids for whom an ultrasound report from the last two years cannot be obtained may undergo transvaginal ultrasound at the screening visit to confirm the presence of one or more fibroids.

2. INTRODUCTION

Relugolix is a daily, orally active, potent, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) (relugolix combination therapy) for the treatment of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Relugolix competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are considerably reduced, with the reduction in FSH concentrations preventing natural follicular growth and development, limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Further, prevention of an LH surge inhibits ovulation, and therefore the corpus luteum does not develop, which precludes the production and secretion of progesterone into the systemic circulation. Relugolix is combined with E2 1 mg and NETA 0.5 mg to maintain E2 concentrations within a therapeutic range and progesterone/progestin concentrations at low levels, to treat symptoms associated with endometriosis and uterine fibroids while maintaining bone mineral density (BMD) and preventing vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen.

Relugolix combination therapy is intended to provide an effective and well-tolerated option for the long-term treatment of symptoms associated with endometriosis and uterine fibroids. This study will evaluate the efficacy and safety of relugolix combination therapy as a contraceptive in women with a diagnosis of uterine fibroids or endometriosis.

2.1. Study Rationale

Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Uterine fibroids and endometriosis are both prevalent conditions in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy or safety of participants undergoing treatment with relugolix combination therapy for the treatment of symptoms associated with endometriosis or uterine fibroids. This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis.

This study is being conducted in women of reproductive age with endometriosis or uterine fibroids and presumed normal fertility. By determination of the Pearl Index (PI) for relugolix combination therapy (ie, by quantifying the contraceptive effectiveness), the study will provide evidence for participants and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception during treatment with relugolix combination therapy.

2.2. Background

Replicate, randomized, double-blind, placebo-controlled, 24-week phase 3 studies followed by a long-term open-label extension study were conducted within each indication to support marketing approval. Relugolix combination therapy has been approved in the United States as MYFEMBREE® for the management of heavy menstrual bleeding associated with uterine fibroids.

To support the uterine fibroid indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with heavy menstrual bleeding associated with uterine fibroids. Patients with confirmed uterine fibroids with heavy menstrual bleeding were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (Studies MVT-601-3001 [N = 387] and MVT-601-3002 [N = 381]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open label- extension study (MVT-601-3003), designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the uterine fibroid indication.

A statistically greater proportion of women treated with relugolix combination therapy compared to placebo (73.4% vs. 18.9% [$p < 0.0001$] in MVT-601-3001 and 71.2% vs. 14.7%% [$p < 0.0001$] in MVT-601-3002) achieved the primary endpoint of both a menstrual blood loss volume of < 80 mL and at least a 50% reduction from baseline in menstrual blood loss (MBL) volume over the last 35 days of treatment. Six key secondary endpoints related to menstrual blood loss volume, amenorrhea, change in hemoglobin, pain associated with uterine fibroids as measured by a Numerical Rating Scale, and change in patient-reported distress from heavy bleeding, passing of blood clots, and pelvic pressure as assessed by the validated Bleeding and Pelvic Discomfort scale, and change in uterine volume were also met. Relugolix combination therapy maintained BMD at levels comparable to placebo over 24 weeks and was generally well tolerated. Additionally, the long-term extension study MVT-601-3003 demonstrated durability of treatment effect for up to 52 weeks. The overall safety profile of relugolix combination therapy for up to 52 weeks was consistent with that observed over the first 24 weeks with low incidence of vasomotor symptoms and maintenance of BMD over time.

To support the endometriosis indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 1250 premenopausal women with pain associated with endometriosis. Patients with confirmed endometriosis with moderate to severe pain were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (MVT-601-3101 [N = 628] and MVT-601-3102 [N = 622]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3103) designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the endometriosis indication.

Patients receiving relugolix combination therapy achieved both co-primary endpoints by demonstrating clinically-meaningful pain reductions compared to placebo for dysmenorrhea (74.5% vs. 26.9% [$p < 0.0001$] in MVT-601-3101 and 75.2% vs. 30.4% [$p < 0.0001$] in

MVT-601-3102) and for nonmenstrual pelvic pain (58.5% vs. 39.6% [p < 0.0001] in MVT-601-3101 and 66% vs. 42.6% [p < 0.0001] in MVT-601-3102).

In study MVT-601-3101, all seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, and impact of pain on daily activities as measured by the Endometriosis Health Profile-30 (EHP-30) pain domain, greater proportions of women not using analgesics (p-values < 0.0001), changes in mean nonmenstrual pelvic pain (p = 0.0002), greater proportions of women not using opioids (p = 0.0005), and changes in mean dyspareunia (painful intercourse; p = 0.0149). In study MVT-601-3102, six of seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, impact of pain on daily activities as measured by the EHP-30 pain domain, a greater proportion of women not using opioids (all p-values < 0.0001), changes in nonmenstrual pelvic pain (p = 0.0012), and dyspareunia (painful intercourse; p = 0.0371). Relugolix combination therapy was generally well tolerated with minimal BMD loss over 24 weeks.

In addition, an ovulation inhibition study with relugolix combination therapy in healthy adult premenopausal women has been completed (MVT-601-046, N = 67). This open-label, single-arm study included a pre-treatment period to confirm ovulatory status, an 84-day treatment period to assess the effects of relugolix combination therapy on ovarian activity, and a post-treatment follow-up period to determine time to return of ovulation. Ovulation (as assessed by the Hoogland-Skouby scale [Hoogland and Skouby 1993]) was inhibited for 100% of participants during the entire 84-day treatment period, and ovarian activity, as evidenced by the degree of follicular growth, was markedly suppressed. Pituitary secretion of FSH and LH, and ovarian production of estradiol and progesterone were markedly suppressed with relugolix combination therapy, with median E2 serum concentrations consistently maintained within an approximate range of 30 to 40 pg/mL during the 84-day treatment period. Mean progesterone concentrations were consistently maintained between 0.94 and 1.25 nmol/L, with individual values all below 5 nmol/L, the cut-off value for luteal activity in the Hoogland-Skouby assessment scale, consistent with the suppression of ovulation observed across all three treatment periods. Additionally, endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness consistently maintained between 4 and 5 mm and likely contributing to the reduction in overall bleeding. All women returned to ovulation or began menses upon discontinuation of relugolix combination therapy demonstrating the revisability of the treatment effect. The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days, with 97.01% (65 of 67 participants) having a confirmed ovulation within 36 days post treatment (one participant ovulated on Day 43 and the other began menstruation on Day 39).

As of June 2021, the relugolix clinical development program includes data from 4463 participants and patients exposed to relugolix either as monotherapy or as relugolix combination therapy, and includes 2554 patients exposed for at least 6 months and 1545 patients exposed for at least one year. These data include single doses up to 360 mg and multiple doses up to 120 mg administered for more than a year. Data from the pivotal phase 3 studies in the uterine fibroid indication demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. Data from the pivotal phase 3 studies in the endometriosis indication also demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo.

These collective data continue to support a favorable benefit/risk profile for the proposed indications.

In summary, data from the relugolix nonclinical, pharmacodynamic, and clinical development program support the proposed mechanism of action for relugolix combination therapy, which works through inhibition of follicular development and prevention of ovulation, suppressing the secretion of endogenous estradiol and progesterone. Data from the completed pivotal phase 3 studies demonstrate robust efficacy results for the indications studied. Data from the ovulation inhibition study demonstrate maximal suppression of ovulation. The currently available safety database is large and allows characterization of the safety profiles of relugolix monotherapy and relugolix combination therapy to support initiation of this study. A detailed description of the chemistry, pharmacology, efficacy, and safety of relugolix is provided in the investigator brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of relugolix combination therapy may be found in the current investigator brochure.

2.3.1. Risk Assessment

On the basis of nonclinical studies, clinical safety analyses, and data available for investigations of similar compounds, relugolix combination therapy may be associated with potential risks. The risk assessment and mitigation strategies for this protocol are outlined in Table 2.

Table 2: Study MVT-601-050: Risk Assessment and Mitigation Strategies

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Identified Risk		
Uterine fibroid prolapse or expulsion.	Exclusion of participants with abnormal bleeding due to uterine fibroids or known submucosal uterine fibroids.	Active monitoring of adverse events.
Potential Risk		
Decreased Bone Mineral Density 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.	Exclusion criteria for: - History of osteoporosis, history of treatment for low BMD, current osteoporosis, or low BMD (Z-score $\leq$-2.0 at lumbar spine, total hip, or femoral neck during the screening period), - History of or current metabolic bone disease, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, 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 BMD eligibility criteria for the study are allowed	Bone mineral density will be monitored at the Baseline, 6-Month, and 12-Month/Early Termination visits with specified discontinuation criteria. There will then be a post-treatment follow-up period with BMD measured again at 6- and 12- months after treatment (PTFU DXA Month 6 and Month 12). Active monitoring of bone health events will be performed.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Hepatic Transaminase Elevation Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver biochemical tests (ALT and or AST ≥ 3 x ULN) are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 × ULN; total bilirubin values > 1.5 × ULN.	Hepatic transaminases are monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009) in all relugolix studies. Abnormal liver tests (AST or ALT ≥ 3 × ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.
Embolic and Thrombotic Events Oral contraceptives and hormone replacement therapy are associated with an increased risk for a venous or arterial thromboembolic event.	Exclusion of participants with previous or current venous thromboembolism.	Active monitoring of adverse events.
Embryofetal Toxicity In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures similar to those at the recommended human dose. No effects on embryofetal development were observed in rats in a similar study. In both rabbits and rats, no fetal malformations were present at any dose level tested that were associated with relugolix exposures similar to and approximately 733-times the exposures in women at the recommended human dose, respectively. Based on these findings, exposure to relugolix combination therapy early in the first trimester of pregnancy has the potential to increase the risk of early pregnancy loss.	Exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Tumors (Breast and Liver) Breast cancer is a hormonally sensitive tumor. There is substantial evidence that combined oral contraceptives do not increase the incidence of breast cancer. Although past studies have suggested that combined oral contraceptives might increase the incidence of breast cancer, more recent studies have not confirmed such findings. Hepatic adenomas are associated with hormonal contraceptive use and a long-term increased risk of developing hepatocellular carcinoma.	Exclusion criteria for participants with known, suspected, or a history of breast cancer or active liver disease.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase. Active monitoring of adverse events.
Mood Disorders Depression has been reported with the prescribed use of GnRH receptor antagonists and agonists and with combined oral contraceptives and hormone replacement therapy.	Exclusion of participants whose mood disorder has been unstable or not well controlled. Exclusion of participants who have major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria. Exclusion of participants with history of suicidal ideation or suicidal behavior.	Active monitoring of adverse events.
Gallbladder Disease Combined hormonal therapy use may be associated with gallbladder disease.	Exclusion criteria for ALT and AST > 2 × ULN; total bilirubin values > 1.5 × ULN.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase and adverse events is performed during the treatment period.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMD = bone mineral density; DXA = dual-energy X-ray absorptiometry; FDA = Food and Drug Administration; GnRH = gonadotropin-releasing hormone; PTFU = post-treatment follow-up; ULN = upper limit of normal.

Adverse drug reactions associated with relugolix combination therapy in women with uterine fibroids include the nonserious adverse events of hot flush, abdominal pain, uterine bleeding, alopecia, libido decreased, irritability, hyperhidrosis, dyspepsia, and breast cyst and serious adverse events of uterine myoma prolapse and expulsion. Adverse drug reactions associated with relugolix combination therapy in women with endometriosis include the nonserious events of headache, hot flush, hyperhidrosis, back pain, arthralgia, libido decreased, metrorrhagia, and vulvovaginal dryness.

In completed phase 1, 2, and 3 studies, there were no drug-specific trends observed in mean or individual patient vital sign measurements, laboratory test results, or electrocardiogram parameters, with the exception of infrequent transient and predominantly mild hepatic transaminase elevations that were observed at a frequency comparable to that in placebo.

No new safety concerns have been identified during active ongoing monitoring.

Overall, the benefit/risk profile remains favorable for the continued development of relugolix combination therapy.

2.3.2. Benefit Assessment

Relugolix combination therapy is a once daily oral medication that has been shown to achieve 100% suppression of ovulation in an ovulation inhibition study (MVT-601-046), suggesting that with appropriate use it has the potential to be a highly effective contraceptive method. Additionally, prompt resumption of ovulation following discontinuation of relugolix combination therapy was observed, indicating the return to fertility is rapid and predictable.

The contraceptive action of relugolix combination therapy is mediated by relugolix, which suppresses follicular development and endogenous production of estrogen and progesterone. The risks of bone loss and vasomotor symptoms associated with a hypoestrogenic state, as well as endometrial hyperplasia from unopposed estrogen, are mitigated by administering relugolix in combination with E2 and NETA at low doses commonly used for hormone replacement therapy in menopause rather than the higher doses used in combined hormonal contraceptives to suppress ovulation. The low dosing of E2 and NETA in relugolix combination therapy may be considered an advantage to those who prefer to minimize the use of exogenous hormones.

Similar to continuous or extended cycle oral contraceptive regimens, relugolix combination therapy may benefit women who wish to limit cyclic bleeding for personal reasons. In the uterine fibroid studies, relugolix combination therapy was associated with an 84.3% reduction in menstrual blood loss volume and a high proportion of patients achieved amenorrhea (52.3% in MVT-601-3001 and 50.4% in MVT-601-3002). This change in the menstrual bleeding pattern may be considered as an advantage to some women.

Relugolix combination therapy has been generally well tolerated in most patients and participants, with an overall low rate of discontinuation due to adverse events.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with relugolix combination therapy are justified by the

anticipated benefits that may be afforded to participants in this study who seek effective contraception.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 3.

Table 3: Study MVT-601-050 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in women with uterine fibroids or endometriosis who are18 to 50 years of age and at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.

Objectives	Endpoints
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To evaluate change in bone mineral density during treatment with relugolix combination therapy.	• Percent change in bone mineral density from baseline to 6 and 12 months on-treatment at lumbar spine (L1-L4), total hip, and femoral neck.
• To evaluate post-treatment change in bone mineral density.	• Percent change from baseline and 12 months on-treatment (or Early Termination) to the 6-month and 12-month post-treatment time points at lumbar spine (L1-L4), total hip, and femoral neck.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

4. STUDY DESIGN

4.1. Overall Design

This is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy. Approximately 1020 sexually active women with uterine fibroids or endometriosis who are18 to 50 years of age and will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

After participants sign the informed consent form (ICF), their eligibility will be assessed at Screening/Visit 1 (see Schedule of Activities; Table 1). A history of either uterine fibroids and heavy menstrual bleeding or endometriosis with moderate to severe pain will be confirmed.

A participant will be considered to have a history of fibroids if there is documentation of an ultrasound from the last two years showing one or more fibroids and the patient reports heavy menstrual bleeding affecting quality of life. If documentation of an ultrasound cannot be obtained, then an ultrasound may be performed locally to confirm the presence of one or more fibroids. Participants with fibroids will be asked a single question about their menstrual flow to determine eligibility (see Section 8.1.2).

Participants entering with a diagnosis of endometriosis-associated pain must have documentation of directly visualized endometriosis (either on laparoscopy or laparotomy) or histologically-confirmed endometriosis. They will be asked two questions at enrollment to determine eligibility (see Section 8.1.2).

After a thorough review of the participant's medical history, gynecological history including contraception, and use of prior medications, their height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy. Participants who are 40 years of age or older at the time of enrollment will need to undergo a screening mammogram locally (see Section 8.2.7. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial), if no normal result is available from an examination within 18 months prior to screening. Screening tests for the sexually transmitted diseases (STD) gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible for rescreening once they have received adequate treatment for the identified STD (see Section 8.1.2). Participants who are noted to have vitamin D deficiency (12-19 ng/mL) may be supplemented with calcium and vitamin D at the discretion of the treating clinician. Participants who fail screening due to vitamin D levels < 12ng/mL may begin supplementing and subsequently be rescreened at the discretion of the treating clinician. Participants who are supplementing with vitamin D based on low screening vitamin D level or are re-screened after vitamin D supplementation and subsequently enrolled should then have a vitamin D level drawn at Visit 3 (see Table 1). The treating clinician can manage further supplementation based on this repeat level.

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 1b, which will consist of a BMD assessment via dual-energy X-ray absorptiometry (DXA) scan, which should be done between 30 and 15 days prior to Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies.

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. Home pregnancy tests will be provided for assessment prior to each cycle as required by the study and as needed during the cycle.

If Visit 2 occurs on Days 1-3 of the menstrual cycle for participants not using any contraceptive method or using barrier contraception, or within the appropriate window for participants transitioning from another contraceptive method, the participant will begin her first treatment cycle of relugolix combination therapy by dosing with study medication at Visit 2. If the visit is not within the window to begin dosing, the participant will be dispensed the study intervention for initiation at home. When the participant reports the onset of the next menses in the eDiary or reaches the appropriate window to begin dosing if transitioning from another contraceptive method, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention. The first dose of study intervention will be confirmed

by a phone visit. Once dosing of study intervention begins, the eDiary is organized by 28-day treatment cycles (ie, Cycle 1, 2, 3….), which are successive periods of 28 consecutive days. The eDiary continues with daily questions related to the intake of study intervention. At the end of each 28-day treatment cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding treatment cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding treatment cycle. Each subsequent treatment cycle starts with the result of a home pregnancy test, which must be negative and must be entered in the eDiary for a participant to continue in the study.

Participants will return to the clinic in the first week after completion of Cycle 1 for Visit 3. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Other records in the eDiary will be assessed, including use of other forms of contraception, occurrence of sexual intercourse during the first cycle (recorded once, at the end of the cycle), results of home pregnancy tests (if applicable), and the result of the protocol-required home pregnancy test prior to the start of Cycle 2. The occurrence of adverse events and use of concomitant medication since the last visit will be assessed. Body weight and vital signs will be measured. Blood tests will be obtained. A vitamin D level should be obtained if the treating clinician started supplementation based on vitamin D deficiency. Further supplementation following a normal repeat level will be left up to the discretion of the treating clinician. Study medication will be dispensed. Approximately 6 weeks after Visit 3, a telephone contact will be made (Phone 3; see Table 1), focusing on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable.

On-treatment site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur in the first week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Approximately 6 weeks following each on treatment site visit, the participant will be contacted by telephone (Phone 4, Phone 5, and Phone 6). The site visits will have the same assessments described for Visit 3 above. The telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last on-treatment visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

On-treatment DXA scans are to be completed at 6 and 12 months (± 30 days). The 12-month on-treatment scan should be done as close to 12 months as possible, but may be completed up to the time of Visit 7.

Fourteen days after completion of Cycle 13, or after early discontinuation of treatment, participants will return to the clinic for the follow-up/ end-of-treatment (EOT) visit (Visit 7). All assessments done at on-treatment visits will be repeated. In addition, physical, gynecological, and breast examinations will be conducted, and blood samples will be obtained for lab tests along with serum β-hCG to determine pregnancy. A mammogram will be performed, if indicated. Post-treatment contraception will be discussed and any remaining study medication and the eDiary will be collected.

Any participant who has an on-treatment pregnancy or is pregnant at the follow-up/EOT visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Two post-treatment follow-up (PTFU) DXAs will be performed at 6 months and 12 months (PTFU Month 6 and PTFU Month 12), with a limited set of serum labs (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphate) if BMD loss meets prespecified criteria of > 3% loss at any anatomic site or a participant has a Z-score of $\leq$ -2.0.

4.2. Scientific Rationale for Study Design

This is an open-label, single-arm, phase 3 study designed to demonstrate the contraceptive efficacy of relugolix combination therapy in the intended treatment population. The primary objective is to assess the contraceptive efficacy of relugolix combination therapy in women with uterine fibroids or endometriosis who are 18 to 50 years of age and are at risk for pregnancy, as expressed by the At-Risk PI in the restricted intent-to-treat (rITT) population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse. Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles") for a total duration of 52 weeks.

To demonstrate the intrinsic contraceptive efficacy of relugolix combination therapy, a study population of women with uterine fibroids or endometriosis without known impaired fertility is considered adequate if patients have regular menstrual cycles (ie, presumed regular ovulation). To support a proper assessment, women participating in this study should be sexually active with men and should agree to abstain from using other forms of contraception during the treatment period.

Participants will visit the study site approximately every 12 weeks for safety evaluations, which include review of adverse events, eDiary, and concomitant medications, and collection of weight, vital signs (blood pressure, heart rate), and urine pregnancy test. Clinical laboratory evaluations will occur at Visits 1, 3, 4, 5, 6 and 7. The study eligibility criteria were designed to minimize risk to participants and rules for evaluation of liver test abnormalities, consistent with FDA guidance (FDA 2009), have been incorporated into the protocol.

4.3. Justification for Dose

The relugolix combination therapy doses of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg were selected for this study as they are the proposed clinical doses in women with heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

In replicate pivotal phase 3 trials, within each of the indications studied, a 40-mg dose of relugolix combined with E2 1 mg and NETA 0.5 mg resulted in marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women and a decrease in pelvic pain associated with endometriosis, respectively. Across the development programs, the combination of relugolix with E2 and NETA at the selected doses demonstrated maintenance of BMD and prevented vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen. Across all studies, relugolix

combination therapy was generally well tolerated in most participants, with an overall low rate of discontinuation due to adverse events. On the basis of the favorable benefit-risk profile observed in each indication, Myovant intends to commercialize relugolix combination therapy for the treatment of heavy menstrual bleeding associated with uterine fibroids and for pain associated with endometriosis.

In a study evaluating the effects of relugolix combination therapy on ovarian activity in healthy premenopausal women (MVT-601-046), relugolix combination therapy demonstrated inhibition of ovulation, as determined by Hoogland-Skouby score, in 100% of women receiving relugolix combination therapy during the entire 84-day treatment period. Therefore, these same doses are expected to be effective in preventing pregnancy.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed thirteen 28-day treatment cycles, the safety follow-up/ EOT visit (Visit 7), and the PTFU Month 6 and Month 12 DXAs (refer to Schedule of Activities, Table 1).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 50 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a diagnosis of uterine fibroids or endometriosis meeting *either* of the below criteria:
    a. Diagnosis of uterine fibroids by confirmation of ultrasound performed in the last 2 years (submucosal fibroids > 50% intracavitary are excluded) and patient report of heavy menstrual bleeding affecting quality of life.

       Note: If an ultrasound report from the last 2 years cannot be located, the participant should undergo transvaginal ultrasound at the time of screening to confirm the presence of one or more uterine fibroids.

    b. Diagnosis of endometriosis and has had, prior to signing the informed consent form, surgical or direct visualization (laparoscopy or laparotomy) and/or histopathologic confirmation of endometriosis, and during the Screening visit, the

patient reports moderate, severe, or very severe pain during the most recent menses and/or during nonmenstrual portion of the cycle in the prior month;

6. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
7. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through end of treatment;
8. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
9. Has body mass index (BMI) ≥ 18 kg/m2;
10. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

5.2. Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:
    a. Vascular disease (eg, cerebrovascular disease, coronary artery disease, peripheral vascular disease);
    b. Women over 35 who smoke;
    c. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation);
    d. Inherited or acquired hypercoagulopathies, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant);

    Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

   Note: The specific reasons for exclusion should be documented in the interactive web-response system (IWRS).

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Malabsorptive disease (including, but not limited to, inflammatory bowel disease and gastric bypass surgery);
11. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

    Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

12. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);

b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula

c. Fasting triglycerides > 150 mg/dL;

d. High-density lipoprotein level < 50 mg/dL.

13. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

14. Has a known history of infertility or subfertility (examples include but are not limited to prior ectopic pregnancy, prior surgery of fallopian tube, prior imaging or procedure suggesting non-patent fallopian tube, history of infertility workup or treatments);

15. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;

16. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.

17. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, intermenstrual/bleeding between menstrual periods, bleeding from a cervical polyp, recurrent bleeding after intercourse);

18. Has a known submucosal fibroid (> 50% intracavitary);

19. Women with a diagnosis of endometriosis who have had four or more prior laparoscopic or open abdominal or pelvic surgical procedures for endometriosis.

Other Conditions/Disorders

20. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);

21. Has known HIV infection or high risk of contracting human immunodeficiency virus (HIV) (eg, has multiple sexual partners, intravenous drug use in participant or partner);

22. Has a history of malignancy ≤ 5 years prior to signing the ICF, except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced

malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;

23. Has known BRCA mutation or other mutation associated with increased risk of breast cancer;
24. 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;
25. History of suicidal ideation or suicidal behavior;
26. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants 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 or mental health professional's judgement, 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 treatment period should not be enrolled;
27. Has a hepatic hemangioma, or has a history of cholestasis with prior estrogen use or during pregnancy;
28. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
29. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
30. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

31. Has a known or suspected pregnancy;
32. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
33. Is breastfeeding or has breastfed in the last year.

At risk of bone loss or unable to be monitored for changes in bone density

34. Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur (eg, bilateral hip replacement, spinal hardware in the lumbar spine);
35. Has a bone mineral density Z-score $\leq$ -2.0 at lumbar spine, femoral neck, or total hip during the screening period;

36. Screening 25-OH-Vitamin D level < 12 ng/mL (patients with vitamin D deficiency with levels 12-19 ng/mL are permitted if supplementing with vitamin D).

    Note: If patients fail screening because of vitamin D levels, they may begin supplementing with vitamin D at the discretion of the treating clinician and be re-screened eight weeks later.

37. Has a history of or currently has osteoporosis, or other metabolic bone disease, collagen vascular disease, chronic kidney disease (CKD) stage 3 or greater with glomerular filtration rate (GFR) < 60 mL/min/m^2 using Modification of Diet in Renal Disease (MDRD) method, hyperparathyroidism, hyperprolactinemia, known pituitary adenoma, hyperthyroidism, anorexia nervosa, abnormal bone mineral metabolism (eg, hypophosphatemia), or low traumatic (fragility) fracture. 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;

38. Past history of use or current use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;

39. Prior use of depo-medroxyprogesterone acetate for a treatment period > 2 years.

Concomitant and Recent Medications/Devices

40. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);

41. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;

42. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein);

43. Has used chronic glucocorticoids that are oral, parenteral, inhaled (prednisone equivalents of ≥ 2.5mg daily for ≥ 3 months) in 12 months prior to the study. Women with epidural or spinal glucocorticoid use at any dose in the last 12 months are excluded.

Miscellaneous

44. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

5.3. Lifestyle Considerations

No restrictions are required for treatment with relugolix combination therapy.

5.4. Screen Failures

Participants who consent to participate in the clinical study but are not subsequently entered in the study are considered to have had a screen failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the

Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any serious adverse event.

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Note: the study intervention in this study is relugolix combination therapy, also referred to as either relugolix combination therapy, study medication, or study drug.

6.1. Study Intervention(s) Administered

Fixed-dose combination (FDC) tablets, each consisting of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg will be supplied as immediate-release, yellow, film-coated tablets. In addition to the three active pharmaceutical ingredients, the core tablet formulation consists of compendial grade excipients including mannitol, lactose monohydrate, sodium starch glycolate, hydroxypropyl cellulose, and magnesium stearate.

The study intervention is presented in Table 4.

Table 4: Study MVT-601-050 Study Intervention

Intervention Name	**Relugolix Combination Therapy**
Type	Drug
Dose Formulation	Round film-coated yellow tablet
Unit Dose Strength	FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg)
Dosage Level(s)	Single FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg) QD
Route of Administration	Oral
Use	Experimental
IMP/NIMP	IMP
Sourcing	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee
Packaging and Labeling	Study intervention will be provided in a blister package. Each will be labeled as required per US requirements.

Abbreviations: E2 = estradiol; FDC= fixed-dose combination; IMP = investigational medicinal product; NETA = norethindrone acetate; NIMP = non-investigational medicinal product; QD = once daily; US = United States.

6.2. Preparation/Handling/Storage/Accountability

Relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablets are supplied to the study site in blister cards with 28 tablets. The FDC tablets should be stored in the original closed blister card.

All study participants will take study intervention comprising one tablet daily at approximately the same time.

If a dose is missed, instructions are as follows:

- If a dose is missed and the error is recognized on the same calendar day, the study intervention should be taken as soon as possible, and then regular dosing should be resumed the next calendar day at the usual time.
- If the missed dose is not recognized until the next calendar day (one missed dose), the dose intended for that calendar day should be taken as soon as possible, and regular dosing should be resumed the following day at the usual time.
- If 2 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time.
- If 3 to 6 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time. Back-up contraception should be used for 7 days.
- If 7 or more consecutive days are missed, the participant should begin using back-up contraception immediately and should be seen for an unscheduled visit. The medical monitor should be contacted.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. Although participants and investigators are not blinded to the study treatment or the study outcome (pregnancy), bias is limited because the diagnosis of pregnancy is an objective measure.

6.4. Study Intervention Compliance

Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles"), for a total duration of 52 weeks (364 days). Participants should complete their eDiary each day on study and should bring all remaining study intervention and all used study intervention packages to each study visit. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for dose interruptions will also be recorded in the eCRF.

6.5. Concomitant Therapy

Concomitant or prior therapies must be recorded including:

- Any medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements) from signing the ICF through the end of the study; or
- Any vaccine, immunization, or hormonal contraceptive method from 6 months prior to signing the ICF through the end of the study;

This information must be recorded in the following ways:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Medications

Table 5 provides examples of prohibited drug categories and windows of exclusion prior to screening; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding participant use of a particular drug or drug class.

Table 5: Study MVT-601-050 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class and Effect	Examples	Window/Comments
Bisphosphonates	alendronate etidronate zoledronic acid	Any past use is exclusionary.

Drug Class and Effect	Examples	Window/Comments
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Any past use is exclusionary. Calcium and vitamin D2 and vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	3 months Note: All other anticonvulsants are allowed.
P-glycoprotein inhibitors and/or moderate or strong CYP3A inhibitors	amiodarone azithromycin[a] carvedilol[d] clarithromycin[a] cobicistat cyclosporine[b] dronedarone erythromycin[a] gentamicin glecaprevir/pibrentasvir indinavir itraconazole ketoconazole lapatinib propafenone quinidine ranolazine ritonavir sofosbuvir/velpatasvir/ voxilaprevir tetracycline verapamil[c] vemurafenib	14 days or 5 times the elimination half-life, whichever is longer (6 months for amiodarone) For participants requiring a short course of these drugs during the treatment period, investigator must contact the medical monitor for approval and guidance on study intervention administration during this period.

Drug Class and Effect	Examples	Window/Comments
Combined p-glycoprotein and strong CYP3A inducers	carbamazepine lumacaftor mitotane phenobarbital phenytoin rifampin rifapentine St. John's wort	28 days
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of greater than or equal to 2.5 mg every day during the study. Note: Spinal or epidural glucocorticoids are prohibited at any dose. Topical, 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. Washout period 12 months
Hormonal contraceptive pills, patches, and vaginal rings	combined or progestin-only Nuva Ring®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3.
Long-acting injectable hormonal contraceptives	depot medroxyprogesterone acetate	Prior use > 2 years is exclusionary. If use is < 2 years, washout period is 24 months.
Progestin implants and intrauterine devices	Nexplanon® Mirena® Paragard®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3.

Drug Class and Effect	Examples	Window/Comments
GnRH antagonists/agonists	leuprolide acetate injection, such as leuprorelin or goserelin acetate injections elagolix	3 months (6 months for 3-month injections)
Anti-androgens	danazol	4 months
Aromatase inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3]; 6 months for depot subcutaneous or intramuscular injections)
Selective estrogen receptor modulators	raloxifene bazedoxifene asofoxifene clomifene tamoxifen	2 months
Selective progesterone receptor modulators	mifepristone ulipristal acetate	6 months
Proton pump inhibitor	omeprazole esomeprazole pantoprazole	3 months
Anti-coagulants/ platelets/fibrinolytics	warfarin heparin low molecular weight heparin clopidogrel tranexamic acid vitamin K preparations Factor Xa inhibitors	3 months

Drug Class and Effect	Examples	Window/Comments
SGLT-2 inhibitors/	ertugliflozin dapagliflozin empagliflozin canagliflozin	3 months
Thiazolidinediones	rosiglitazone pioglitazone	3 months

Abbreviation: GnRH = gonadotropin-releasing hormone.
a. Roxithromycin is allowed.
b. Tacrolimus is allowed.
c. Amlodipine, felodipine, and nifedipine are allowed.
d. Metoprolol and atenolol are permitted.

6.6. Dose Modification

The dose level of relugolix combination therapy cannot be modified because it is administered as a single daily tablet.

Participants 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. Back-up contraception should be advised, as appropriate. Participants may subsequently be re-started on study intervention with the written approval of the sponsor (or designee).

6.7. Intervention After the End of the Study

Not applicable to study MVT-601-050.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Any adverse event that is intolerable to the participant 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 participant if dosing continued;
- If it is discovered after enrollment that a participant failed to meet protocol entry criteria and continued participation would pose an unacceptable risk to their health;
- If the following liver test abnormalities develop, study intervention should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until their laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 × ULN; or

  - ALT or AST > 5 × ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QTc corrected using Fridericia's formula (QTcF) prolongation of more than 500 msec on an electrocardiogram done as part of patient care outside of the study protocol;
- If the patient experiences a fragility fracture or develops a Z-score ≤ -2.0 or > 3% loss of BMD at lumbar spine, total hip, or femoral neck compared with the baseline measurement during study participation. A second DXA scan will be conducted within 30 days and the two DXA results will be averaged. If the average after repeat confirms this level of bone loss, these patients will need to discontinue the study medication and should remain in the trial for PTFU DXA assessments (see Section 8.2.6);
- Participants who are, in the opinion of the investigator or medical monitor, grossly noncompliant with the protocol requirements. Gross noncompliance includes < 75% compliance with the study intervention over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive visits) with < 50% of the required number of eDiary entries. Investigators will follow-up with the participant to encourage compliance with study intervention or eDiary prior to discontinuing her from the study;
- If the participant becomes pregnant at any time after signing the ICF, she must be withdrawn immediately (see Section 8.3.5 for information on pregnancy reporting).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. The medical monitor should be consulted in advance of withdrawal whenever possible.

At the time of discontinuing from the study, an EOT visit should be conducted, if possible. See the Schedule of Activities (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed, including post-treatment DXA scans and serum labs.

The participant will be permanently discontinued from the study intervention at that time.

The participant retains the ability to remain in the study for post-treatment bone density follow-up as per protocol.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1). Guidelines to address study conduct related to restrictions arising from the novel coronavirus 2019 global pandemic are addressed in Appendix 8.

8.1. Efficacy Assessments

8.1.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time point as described in the Schedule of Activities (see Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1.2. Screening Period

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, cervical cancer screening) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (see Table 1).

Prior to conducting any screening procedures, participants will be given a full description of the nature and purpose of the study and will be required to provide written informed consent. The investigator or a designated, medically qualified member of the site staff will interview potential participants and establish their eligibility for inclusion. Potential participants will be screened according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively).

The participant's medical history, gynecological history including contraception, and use of prior medications will be reviewed. Menstrual history will be assessed to ensure the participant has a history of regular menstrual cycles every 21 to 35 days when not using hormonal contraception. If the menstrual cycle duration observed during the screening period does not meet eligibility criteria, screening may be extended with approval of the medical monitor.

A history of either uterine fibroids and heavy menstrual bleeding or endometriosis with moderate to severe pain will be confirmed.

A participant will be considered to have a history of fibroids if there is documentation of an ultrasound from the last two years showing one or more fibroids and the patient reports heavy menstrual bleeding affecting quality of life. If documentation of an ultrasound cannot be obtained, then an ultrasound may be performed locally to confirm the presence of one or more fibroids.

At the screening visit, prior to medical review, participants with fibroids will be asked a question about their menstrual flow to determine eligibility. Participants will be allowed to enroll if they answer "yes."

1. **Uterine Fibroid Menstrual Bleeding Severity [UFMBS] (screening)**:Do you have heavy blood flow during your period that makes your quality of life worse?

   No
   Yes

Participants with a diagnosis of endometriosis-associated pain must have documentation of directly visualized endometriosis (either on laparoscopy or laparotomy) or histologically-confirmed endometriosis. They will be asked two questions at enrollment to determine eligibility:

Endometriosis-Associated Pain Severity [EAPS] (screening)
Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button.

1. How would you rate your worst pelvic pain on days you were having your most recent period (meaning, being on your period)?

Absent
Mild
Moderate
Severe
Very Severe

2. During the last month, how would you rate your worst pelvic pain on days you were **not** having your period (meaning, **not** on your period)?

Absent
Mild
Moderate
Severe
Very Severe

Participants with confirmed endometriosis who answer moderate, severe, or very severe to either question are eligible to participate.

The participant's height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including thyroid-stimulating hormone (TSH), parathyroid hormone (PTH), vitamin D, and β-hCG to rule out pregnancy. A mammogram will be obtained, if indicated. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening tests for the STDs gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible to continue screening once they have received adequate treatment for the identified sexually transmitted disease and if the investigator determines the participant is not at high risk for reinfection (eg, because of multiple sex partners or an untreated partner). A baseline bone density assessment will be performed via DXA scan 15-30 days prior to the planned Visit 2. If the screening period is extended by more than 6 weeks for any reason, screening laboratories should be repeated prior to administration of the first dose of study medication. In the event that the screening period is extended, every effort should be made to have the patient undergo DXA scan as close to 15-30 days prior to Visit 2 as possible.

8.1.2.1. Rescreening

Participants who fail screening may be rescreened with approval of the medical monitor. Participants who are screen-failed based for vitamin D level < 12ng/mL may be supplemented with vitamin D and calcium at the discretion of the treating clinician and then be re-screened after eight weeks. The option to continue supplementation during the study is left to the discretion of the treating clinician. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

8.1.2.2. 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. Other procedures, including cervical cytology, can be retested once without the permission of the medical monitor if necessary due to technical or logistical issues, such as an inadequate sample. Further retesting or retesting for other reasons requires the approval of the medical monitor.

8.1.3. Treatment Allocation

Participants who meet all eligibility criteria, including history, laboratory test, mammogram if indicated, cervical cytology results, and a normal bone density as determined by DXA scan will return for Visit 2, the timing of which depends on contraceptive status at screening. All use of contraceptives must be discontinued prior to Visit 2.

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an eDiary, which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. The first dose of study intervention will be administered on site at the time of Visit 2 or at home as described below. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact. Home pregnancy tests will be provided for assessment prior to each 28-day treatment cycle as required by the study and as needed during the cycle.

8.1.3.1. Prior Use of Hormonal Contraception, Implants, or Devices

For participants with prior use of hormonal contraception or implantable devices, the first dose of study intervention will be administered at Visit 2.

If the participant is transitioning from combined hormonal contraceptive pills, patches, or rings, she may schedule Visit 2 on the day she would normally initiate a new contraceptive cycle. If the visit cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

If the participant is transitioning from progestin-only pills she must schedule Visit 2 the day after completing treatment and use a back-up method for the first 7 days of relugolix combination therapy.

If the participant is transitioning from a contraceptive implant or intrauterine device, she must schedule Visit 2 the day the implant or device is removed and use a back-up method for the first 7 days of relugolix combination therapy. Note that only participants who have requested removal of their implant or intrauterine device for reasons unrelated to the purpose of enrollment may be considered for participation.

Participants with less than two years of use of long-acting injectable contraceptive methods are not eligible to screen for the study until 24 months following their last dose.

8.1.3.2. No Prior Contraceptive Use or Use of Barrier Methods

If the participant was not using any prior contraceptive method or was using barrier contraception (diaphragm, cervical cap, male condom, female condom, or spermicidal foam, sponges, and film), she may schedule Visit 2 on Days 1-3 of the menstrual cycle and the first dose of study intervention will be administered the day of the visit. If the visit cannot be reliably scheduled within the window to begin dosing, the visit should be scheduled prior to the onset of menses. Visit 2 procedures will be conducted, and the participant will begin daily eDiary entries related to the onset of menses. When the participant reports the onset of the next menses in the eDiary, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

8.1.4. Treatment Period

Once dosing of study intervention has been initiated, participants will take their study intervention QD. Dosing of study intervention will be organized by "cycles" of successive periods of 28 days. Participants will self-administer study intervention through the completion of Cycle 13. Participants will record compliance with study intervention dosing daily in their eDiary. At the end of each cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding cycle. Each subsequent cycle starts with the result of a home pregnancy test, which must be negative and entered in the eDiary for the participant to continue the study.

8.1.4.1. Site Visits

Participants will return to the clinic the first week after completion of Cycle 1 for Visit 3.

Subsequent site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur 1 week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Study medication will be dispensed at each visit. See the Schedule of Activities (see Table 1) for assessments required for each visit.

8.1.4.2. Telephone Visits

Approximately 6 weeks following each site visit, the participant will be contacted by telephone (Phone 3, Phone 4, Phone 5, and Phone 6). The first telephone contact will occur approximately 6 weeks after Visit 3. Telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

8.1.4.3. 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 participant'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 (hematology and chemistry), urine or serum pregnancy testing, study intervention compliance, and dispensation of study intervention may be conducted as needed. Consult with the medical monitor, if needed, to discuss unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled DXA.

8.1.5. Post-Treatment Period

8.1.5.1. End-of-Treatment Visit

Two weeks after completion of Cycle 13, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on treatment visits will be repeated, and final status assessed; in addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for all labs, as well as serum βhCG to determine pregnancy. A mammogram will be completed, if indicated. A DXA scan will be obtained. Post-treatment follow-up of bone density will be discussed, including time points for post-treatment follow-up DXA at Month 6 and Month 12, and serum labs, if patient meets pre-specified criteria. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

8.1.5.2. Early Termination Visit

If the participant does not complete the study for any reason (including investigator discretion), the reason and circumstances for the participant's early termination must be fully documented. If possible, the assessments specified for the follow-up/EOT visit (Visit 7) should be performed. See Section 8.2.6 for instructions regarding DXA scans associated with early termination. The medical monitor should be consulted in advance of withdrawal whenever possible. Participants who are withdrawn from the study may not be re-enrolled.

8.1.5.3. Pregnancy Visit

If a participant has an on-treatment pregnancy, the site must discontinue the participant from study intervention immediately and have her return for a visit (see Table 1). In addition to the follow-up/EOT procedures (with exception of DXA) the participant will undergo the following diagnostic procedures:

- Quantitative serum pregnancy test (unless pregnancy already confirmed by transvaginal ultrasound);
- Transvaginal ultrasonography to determine gestational age/estimated date of delivery (EDD).

8.1.6. Efficacy Evaluations

Planned time points for efficacy assessments are provided in the Schedule of Activities (see Table 1).

8.1.6.1. Pregnancy Testing

The contraceptive efficacy of relugolix combination therapy will be evaluated using the number of on-treatment pregnancies. On-treatment pregnancies are pregnancies with an estimated conception date (ECD) between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Pregnancy testing is conducted per the Schedule of Activities (see Table 1) as follows:

- A serum β-hCG pregnancy test is performed at Visit 1 and Visit 7. Serum testing is also performed during the treatment period if an on-treatment pregnancy is suspected or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound). A urine pregnancy test is performed at all site visits after screening and as needed;
- A home urine pregnancy test performed by the participant is required prior to the start of each cycle, and the result must be negative to continue on study. Any on-treatment positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound when applicable).

8.1.6.2. Participant eDiary

All participants enrolled in the study will be provided a device with an application for a participant eDiary at Visit 2, along with detailed instructions for its use. Participants will complete daily eDiary entries including compliance with study intervention dosing, occurrence of sexual intercourse, use of back-up contraception, and home urine pregnancy test results. The eDiary data will be reviewed by the study staff on an ongoing basis and at specified time points as noted in the Schedule of Activities (see Table 1).

8.2. Safety Assessments

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), DXA, mammogram, and clinical laboratory tests. Planned time points for all safety assessments are provided in the Schedule of Activities (see Table 1).

8.2.1. Physical Examinations

A complete physical examination, including gynecological and breast examination, will be conducted at Visit 1 and the follow-up/EOT visit (Visit 7). The examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. Height and weight will also be measured and recorded.

All other physical examinations should focus on signs and symptoms reported by the participant to assess for clinically significant changes from the baseline assessment.

The gynecologic examinations at screening will include testing for gonorrhea and chlamydia. Cervical cytology test must be conducted for participants 21 years or older (or who will become 21 years old during the trial) without an available test result from within 18 months years prior to the Screening Visit and submitted to the central laboratory. A repeat test should be performed for inadequate specimen and submitted to the central laboratory.

A bilateral breast examination will be performed at the time of the gynecologic examination.

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

8.2.2. Vital Signs

Vital signs including heart rate and systolic and diastolic blood pressure will be assessed. Vital signs will be measured with the participant in a seated position and should be preceded by at least 5 minutes of rest with the participant in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

Electrocardiograms are not routinely collected during the study and are to be performed per general clinical safety assessment, as applicable.

8.2.4. Clinical Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Table 1) for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within two weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Table 1).

If laboratory values from non–protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, serious adverse event, adverse event, or discontinuation of study intervention), then the results must be recorded in the eCRF**.**

8.2.5. Ultrasound Examinations

Ultrasound examinations are not routinely scheduled throughout this study. In the event that a participant reports a history of fibroids and heavy menstrual bleeding but no documentation of fibroids from the last two years can be obtained, the participant should undergo a transvaginal ultrasound locally to confirm the presence of one or more fibroids.

Ultrasounds will otherwise occur only on an as-needed basis during the study.

8.2.6. 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) at the time points described in the Schedule of Activities (see Table 1). The scans will be read by the central imaging 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 be used at each site and operated in the same scan mode for all scans for an individual patient.

The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study. The following procedures will be followed, per the central imaging laboratory's charter: If all four vertebral levels are not visualized or if a given image set is of insufficient quality to allow proper interpretation, a query will be issued to the investigator to check whether a repeat scan can be performed. If required anatomy is missing from an image and a repeat scan cannot be obtained, it will not be analyzed. Bone density analysis of DXA scans will only be performed when at least 2 evaluable vertebrae are present. In the event that follow-up data are technically inadequate, not compliant with acquisition parameters, unreadable, unable to be re-captured in a timely manner, or electronically/physically missing, the central radiology site will enter "not assessable" into the database.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), total hip, and femoral neck at the baseline, 6- and 12-month on-treatment time points, as well as at 6- and 12-months post-treatment. A limited set of serum labs will be performed if bone mineral density monitoring at any time point demonstrates loss of > 3% compared to pre-treatment baseline or a Z-score of $\leq$ -2.0. Note that a pregnancy test will need to be completed prior to each DXA.

Follow-up of DXA findings will proceed according to the following rules:

- Participants who develop BMD decline (compared to pre-treatment baseline) of > 3% or a Z-score $\leq$ -2.0 at any anatomic site (lumbar spine, total hip, or femoral neck) will undergo repeat DXA scan to confirm this measurement within 30 days of the first DXA scan. The two DXA results will be averaged. If the average after repeat confirms this level of bone loss, the study medication will be discontinued, but the patient will remain in the trial for post-treatment bone mineral density monitoring (see Section 7.1). In addition, they will need to be referred to a bone specialist.
- If at any time during treatment or post-treatment period a bone mineral density loss of > 3% (compared to pre-treatment baseline) is noted and confirmed on a repeat DXA scan (within 30 days) after averaging the two results, the patient will be referred to a bone specialist. The site should send a de-identified summary of the evaluation and management plan to the sponsor once available.

8.2.6.1. Bone Mineral Density Monitoring in the Setting of Early Termination

In the event of early termination due to reasons unrelated to bone density loss, DXA scans should be obtained according to the following rules:

For early termination occurring **prior to completing 6 cycles of study medication**, an early-termination DXA scan is not required. The participant can proceed with PTFU DXA Month 6 and Month 12, along with serum labs if prespecified criteria for bone loss are met.

- For early termination occurring **after completing 6 cycles of study medication**, the patient should complete a DXA at the time of early termination and then PTFU DXA Month 6 and Month 12 and serum labs if prespecified criteria for bone loss are met.

If the 6-month on-treatment DXA was completed within the last 6 weeks and the patient has completed fewer than 8 cycles of study medication, an early termination DXA does not need to be performed and the patient can proceed to PTFU DXA Month 6 and Month 12, along with serum labs, if indicated.

8.2.7. Mammogram

Participants who are ≥ 40 years of age at the time of enrollment will need to undergo a screening mammogram. If a patient turns 40 years old during the trial, she should have a mammogram completed at the end-of-treatment visit. All participants 40 years of age or older at the time of the end of treatment visit will need to undergo a mammogram at that time.

All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 8) and recorded in the eCRF. The following actions will be taken depending on the reading:

- Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;
- Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;
- Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours;
- Patients who have malignant breast lesion(s) or breast carcinoma will not be eligible to participate, per exclusion criteria. If at the end of the study, these patients should be referred to a breast oncologist as soon as possible.

8.2.8. Suicidal Ideation and Behavioral Risk Monitoring

There will be ongoing monitoring of adverse events associated with mood disorders (see also Section 2.3.1).

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency of Collecting Adverse Event and Serious Adverse Event Information

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention. 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 intervention.

All serious adverse events will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event after conclusion of the study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse reports are provided in Appendix 3.

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 participant is the preferred method to inquire about adverse event occurrences.

The participant's eDiary entries 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 this instrument, proper follow-up with the participant 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.

8.3.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All serious adverse events and adverse events of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted. Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators, as necessary.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will review and then file it along with the investigator brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy Reporting

Details of all pregnancies will be collected after the start of study intervention and until the follow-up visit/EOT (Visit 7) (see Schedule of Activities, Table 1).

If a pregnancy is reported, study intervention should be withdrawn immediately, and the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

8.3.6. Adverse Events of Clinical Interest

Adverse events of clinical interest in this study are defined as any increase in ALT or AST $\geq 3 \times$ 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 safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. Additional instructions for evaluating participants with an increase in ALT or AST $\geq 3 \times$ ULN may be found in Appendix 5.

8.3.6.1. Criteria for Temporary Withholding of Study Intervention 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 intervention should be immediately withheld with appropriate clinical follow-up (including repeat laboratory tests, until the participant's laboratory profile has returned to normal/baseline status), and the event reported per Section 8.3.6 and as a serious adverse event if serious adverse event criteria met, including the underlying diagnosis, as available:

- ALT or AST > 8 × ULN; or
- ALT or AST > 5 × ULN and persists for more than 2 weeks; or
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5; or
- ALT or AST > 3 × 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.

8.3.6.2. Criteria for Permanent Discontinuation of Study Intervention in Association with Liver Test Abnormalities

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

1. ALT or AST increases to ≥ 3 × ULN; AND
2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × 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 intervention treatment should be withheld or permanently discontinued as appropriate for the safety of the participant.

8.3.7. Adverse Events Related to Menstrual Bleeding

To ensure consistent reporting, the terms below should be used when participants report alterations from their usual menstrual bleeding pattern that meet adverse event reporting criteria. Select the term that most closely reflects both the volume of the menstrual flow and the frequency/duration/regularity of the bleeding episodes.

- Amenorrhea: Absence of menstrual bleeding

- Spotting Vaginal: Spotting regardless of the frequency/duration/regularity
- Oligomenorrhea: Infrequent bleeding/light or normal volume
- Polymenorrhea: Frequent bleeding/light or normal volume
- Menorrhagia: infrequent or regular frequency bleeding/ heavy volume OR prolonged bleeding regardless of flow volume
- Hypomenorrhea: regular frequency/light volume
- Metrorrhagia: irregular frequency/light or normal volume
- Menometrorrhagia: irregular bleeding/heavy volume

8.3.8. Fracture Events

Any fractures that occur during the treatment period or the 14-day safety follow-up period should be reported on the case report form according to Appendix 6.

8.3.9. Post-Treatment Follow-Up Period

During the post-treatment follow-up period for bone mineral density, information about bone health will be collected, eg, DXA measurements and fracture events. Clinical information about each fracture will be reported according to Appendix 6.

8.4. Treatment of Overdose

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

For this study, the protocol-specified dose of relugolix combination therapy is one tablet once daily. 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 participant for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a safety report form according to Appendix 3 whether or not the overdose is associated with an adverse event;
- Document the quantity of the excess dose as well as the duration of the overdosing in the Overdose eCRF page.

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Health Economics/ Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no hypothesis associated with the primary endpoint.

9.2. Sample Size Determination

9.2.1. Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 10,000 menstrual cycles of drug exposure in participants 18 to 50 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of 13 28-day cycles;
- 40% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 5 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

9.2.2. Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% confidence interval (CI) for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is

assumed with parameter $\theta = 100\lambda T$ where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100-woman years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with FDA Guidance for Industry (FDA 2019).

At least 10,000 menstrual cycles of drug exposure will be achieved. Assuming 70% of menstrual cycles are at-risk and 40% dropout rate (assuming discontinuers will on average contribute 5 cycles of exposure), approximately 1020 participants must be enrolled to achieve at least 7000 at-risk cycles. Additional participants may be enrolled to ensure a minimum of 200 participants completing the study. With 7000 at-risk cycles, the study will have 95% power for the upper limit of the two-sided 95% CI for the Pearl Index to be < 5 in the overall population, assuming that the true Pearl Index is 2 and that a Poisson model is used to achieve the CI.

The study is powered based on the combined patient population of women with uterine fibroids or endometriosis. The study aims to enroll approximately 50% of women with uterine fibroids (with a minimum of 40%) and up to 50% of women with endometriosis(with a minimum of 25%).

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.3. Populations for Analyses

The analysis populations are defined in Table 6.

Table 6: Study MVT-601-050 Analysis Populations

Analysis Population	Description
Enrolled	All participants who have completed the informed consent process, completed screening procedures, and have been allocated to treatment
Intent-to-Treat (ITT)	All participants who receive at least one dose of study intervention
Modified Intent-to-Treat (mITT)	The subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred
Per-Protocol (PP)	The subset of participants in the rITT population with at least one treatment cycle that is also without specific protocol deviations

Restricted Intent-to-Treat (rITT)	The subset of participants included in the ITT population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred

Abbreviations: ICF = informed consent form.

9.4. Statistical Analyses

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be finalized prior to database lock. This section provides a summary of the planned statistical analyses of the endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

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 participants. Categorical data will be summarized by counts and percentages.

The single, final analysis of all efficacy and safety data will occur after approximately 1020 participants have enrolled and been followed for 14 days after cycle 13 or last dose, if not early terminated.

The safety follow-up analysis will occur after participants have completed 12 months post-treatment follow-up, if not early terminated. Safety follow-up analysis will include two post-treatment DXAs to be performed at 6 months and 12 months after the end-of-treatment visit.

9.4.1.1. Handling of Missing Data

At-risk cycles will be considered those cycles in which participants note vaginal intercourse and no birth control methods other than the study drug were used. These two survey questions are asked once in the eDiary at the end of each 28-day cycle. Cycles will not be included as at-risk cycles in the denominator of the PI calculation if the answers to one or both of these survey questions are missing.

If subjects have fewer than 21 days of eDiary entry (< 75% compliance rate) that cycle will not be labeled an at-risk cycle and will not be included as an at-risk cycle in the denominator of the PI calculation.

All cycles in which on-treatment pregnancies occur (regardless of missing eDiary entries or missing survey questions) will be counted as at-risk cycles.

For estimating on-treatment BMD percent change from baseline, to account for any missing BMD assessment at a scheduled visit, a mixed-effects model with repeated measures will be fit to derive the least square means and 95% CI at Month 6 and Month 12. This model will also consider potential confounding effects as covariates such as age at baseline, visit, baseline BMD, race, BMI at baseline, as fixed effects using an unstructured variance-covariance matrix.

Further details on the endpoint analyses including sensitivity analysis, handling of missing data, and statistical methods will be provided in the Statistical Analysis Plan.

9.4.2. Evaluable Cycles and Pearl Index Definitions

Evaluable cycles are defined below and will contribute to the denominator for calculating each type of PI.

- At-Risk PI (primary efficacy endpoint): Cycles without use of any other contraceptive methods and with confirmed vaginal intercourse (At-Risk Cycles).
- Gross PI: On-treatment cycles.
- Modified At-Risk PI: Cycles without use of any other contraceptive methods regardless of occurrence of vaginal intercourse.
- Method Failure PI: At-Risk Cycles without major protocol deviations.

9.4.3. Primary Endpoint

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment:

$$\text{Pearl Index (PI)} = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{number of 28-day at-risk cycles of treatment}}$$

There is no hypothesis associated with the primary endpoint. The primary contraceptive efficacy will be assessed by the point estimate of At-Risk PI and corresponding 95% CI. On-treatment pregnancies are pregnancies with an ECD between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the EDD will be ascertained. The ECD will be calculated as:

$$\text{EDD} - 38 \text{ weeks} = \text{ECD}$$

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses or β-hCG level.

The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse. The numerator and denominator in the At-Risk PI calculation are slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, as the primary contraceptive efficacy analysis, will be conducted using an rITT population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred. The At-Risk PI will be presented together with the two-sided 95% CI calculated based on a Poisson distribution (Benda et al. 2004).

9.4.4. Secondary Endpoints

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution. Specifically:

- The Gross PI will be estimated using the ITT population, defined as participants 18 to 50 years of age at the time of enrollment who have entered the study and have at least one on-treatment cycle.
- The modified PI will be estimated using the modified ITT (mITT) population, defined as the subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred.
- The Method Failure PI will be estimated using the per protocol analysis population, defined as the subset of participants in the rITT population, with at least one treatment cycle that is also without specific protocol deviations. For calculation of the Method Failure PI, only pregnancies with a conception date during at-risk cycles that were also per protocol are included in the numerator.
- Cumulative 1-year pregnancy rate will be calculated on each of the analysis populations by the Kaplan-Meier (KM) survival analysis. All participants will be followed until they either have an outcome of pregnancy or are censored at the time of their last follow-up. The unit of time in the KM analysis will be the cycle, with pregnancies recorded by cycle of conception. Unlike the PI calculations, cycles based on use of adjunctive contraception will not be excluded.

The primary efficacy endpoint will be assessed by subgroups based on selected baseline characteristics (including age, indication, race, BMI, region, etc.), as appropriate. Details will be included in the Statistical Analysis Plan.

9.4.5. Tertiary/Exploratory Endpoint(s)

Not applicable.

9.4.6. Safety Endpoints

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention treatment, and severity. An adverse event reported more than once for a participant is counted once at the maximum severity or strongest relationship to study intervention treatment when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting

predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each 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 bone mineral density lumbar spine (L1-L4), total hip, and femoral neck. The absolute change and percent change from baseline to 6- and 12-month on-treatment time points and associated 95% CIs will be presented for each bone mineral density location. The same analysis will be also performed for the absolute and percent change from baseline to last on-treatment visit (or early termination [ET] visit) to 6- and 12-month post-treatment follow up visits. Additional analyses can be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure, if appropriate. Details will be provided in the Statistical Analysis Plan.

9.4.7. Other Analyses

Not applicable.

9.5. Interim Analyses

No formal interim analyses are planned for this study.

9.6. Data Monitoring Committee

An independent Data Monitoring Committee 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 Monitoring Committee will be outlined in a separate charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/(independent ethics committee) IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosures

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants undergoing rescreening will sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

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

Data Quality Assurance

Documentation Accountability

- All participant data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the completion of the informed consent process by the first participant and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. CLINICAL LABORATORY TESTS

- All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the protocol Schedule of Activities (see Table 1).
- Laboratory requisition forms must be completed, and samples must be clearly labeled with the Participant 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 7.
- Investigators must document their review of each laboratory safety report.
- Local laboratory results are only required in the event that central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7: Study MVT-601-050 Protocol-Required Safety Laboratory Assessments

Chemistry	**Hematology**	**Other**
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin	WBC Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Serum Pregnancy Test (β-hCG) Urine Pregnancy Test Hemoglobin A1C International normalized ratio (INR) Thyroid Stimulating Hormone (TSH) Parathyroid hormone (PTH) 25-Hydroxyvitamin D (Vitamin D3)
Liver tests: Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase LDH	**Lipid Profile**	**Serology**
	Total Cholesterol Low Density Lipoprotein High-Density Lipoprotein Triglycerides	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody Hepatitis D antibody Hepatitis E antibody Epstein-Barr Virus

Abbreviations: β-hCG= beta human chorionic gonadotropin; LDH = lactic acid dehydrogenase; RBC = red blood cells; WBC = white blood cell.

APPENDIX 3. ADVERSE EVENTS DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an adverse event per definition above, then it cannot be a serious adverse event even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient 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 disability/incapacity • 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 with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgement should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include 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.

Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and/or Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event or serious adverse event information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or their representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event or serious adverse event.

Assessment of Intensity

The investigator will make an assessment of intensity for each adverse event and serious adverse event reported during the treatment period and for 14 days after according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). For terms not specified with the CTCAE, the criteria below should be used to determine the grade severity:

Severity 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

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each adverse event.
A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each adverse event, the investigator **must** document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to PHV-Myovant@quintiles.com. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event to PHV-Myovant@quintiles.com.

The investigator may change his/her opinion of causality in light of follow-up information and send a Safety Report Form follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions are to be used for the relationship of the adverse event to study intervention:

- **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.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to PHV-Myovant@quintiles.com within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to IQVIA RDS, Inc. via Paper CRF

- E-mail transmission of the Safety Report Form paper CRF is the preferred method to transmit this information to the global safety database.
- In rare circumstances and in the absence of e-mail or e-fax equipment, notification by telephone is acceptable with a copy of the Safety Report Form data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Safety Report Form within the designated reporting time frames.
- Contacts for serious adverse event reporting follow:

Using a Safety Report Form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study intervention.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Safety Report Form and is as follows:

Site Location	E-mail (Primary Reporting Method)	Fax Number (Secondary Reporting Method)
All Regions	[redacted]	[redacted]

For questions regarding serious adverse event or adverse event of clinical interest reporting, please call:

- North/South America: [redacted]
- Regional toll-free phone and fax lines distributed separately.

The initial report should include:

- Study number (MVT-601-050)
- Site address and number
- Investigator name
- Participant ID number, sex, and age
- Details of study intervention 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 intervention

If the participant 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 intervention 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, stabilization, the event is otherwise explained, or the participant is lost to follow-up. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

APPENDIX 4. COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the pregnancy report form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be a serious adverse event and will be reported as such.
- Any post-study pregnancy related serious adverse event considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female participant who has an on-treatment pregnancy will discontinue study intervention immediately and return for a Pregnancy visit as described in Section 8.1.5.3.

APPENDIX 5. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Study intervention (relugolix combination therapy) should be withheld for any liver test abnormality listed in Section 8.3.6, 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 Table 8, and per the investigations in Table 9. If close monitoring is not possible, study intervention should be withheld even if the results do not meet the criteria for withholding in Section 8.3.6.

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

Table 8: Study MVT-601-050 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	**Frequency for Repeating Liver (ALT, AST, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests**
If ALT or AST ≥ 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 participant is asymptomatic	Frequency may decrease

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

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

Table 9: Study MVT-601-050 Investigations and 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 Table 8; • 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).

Abbreviations: CBC = complete blood count; INR = International normalized ratio.
Note: If the first follow-up test does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

APPENDIX 6. FRACTURES: INFORMATION FOR REPORTING

Study intervention should be discontinued permanently for any fragility fracture (defined as a fracture occurring as a result of a fall from a standing height or less in the absence of major trauma). The classification of fragility fracture specifically excludes fractures of fingers, toes, face, or skull. Any fracture that occurs during the study should be reported to the sponsor using the designated safety report form.

The following information should be reported to the sponsor:

- Bone(s) that was/were fractured;
- Description of the event leading to the fracture and classification of the fracture as either non-fragility or fragility fracture (see definition above);
- Full assessment of patient's risk factors for fracture and/or confounders for bone loss/fracture;
- Treatment required (none, conservative, surgery, etc.);
- Evidence of healing, if any.

APPENDIX 7. BREAST IMAGING REPORTING AND DATA SYSTEM

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 8. GUIDANCE FOR STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The novel coronavirus 2019 (COVID-19) pandemic has impacted the conduct of clinical trials globally. Regional quarantine laws, travel restrictions, and site closures present challenges to normal study conduct and may lead to missed study visits or procedures or an interruption to a patient's study drug supply.

Myovant Sciences has thoroughly reviewed guidance documents from various country and regional regulatory agencies and has put mitigation plans in place to ensure that the safety of patients is maintained, the study continues to be conducted in compliance with Good Clinical Practice (GCP), and risks to the integrity of the study are minimized. These plans will remain in place through the duration of the COVID-19 pandemic.

Safety During the COVID-19 Pandemic

Protecting study patients, investigational site staff and clinical service providers involved in Myovant Sciences clinical studies from activities that may unnecessarily increase the risk of contracting COVID-19 is of utmost importance. Regulations and policies instituted for safety purposes during the COVID-19 pandemic at the institutional, local, country, and regional level should be adhered to.

Protocol Adherence

Wherever possible and safe, study visits and procedures must be performed as outlined in the protocol to ensure patient safety and to maintain the integrity and interpretability of the study data. While modifications to normal study conduct may, in some cases, be necessary and unavoidable, they must be documented and reported where in conflict with the study protocol and this guidance. Deviations from the protocol will be documented, but those resulting specifically from the COVID-19 pandemic will be marked as such. All deviations resulting from the COVID-19 pandemic will be summarized in the clinical study report.

Visit Schedules and Study Procedures

Local policies, institutional restrictions, and/or patient ability/willingness to make site visits may curtail the ability to adhere to the in-person, on-site visit schedule required by the protocol. Investigators at clinical sites should evaluate the appropriateness of an on-site study visit during the COVID-19 pandemic.

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, as close to the visit target date as possible, taking all measures to prevent contracting COVID-19.

- All protocol-required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, Investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.
- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of

the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the Myovant medical monitor for consultation, as necessary.

If the clinical study site is closed or the patient is unable/unwilling to attend on-site study visits due to the COVID-19 pandemic, alternative methods for completing assessments (eg, phone contact or virtual visit) should be implemented.

- Investigators must assess and evaluate the patient's continued participation and dosing with limited safety assessment.
- At a minimum, investigational site staff should make every attempt to contact the patient via telephone when an expected visit is due or missed to assess for adverse events, document concomitant medications, and study drug dosing since the last study visit.
- If the safety blood draws cannot be performed through the central laboratory per protocol, the investigator may advise the patient to have blood drawn at a local laboratory if there is a safety concern. If two consecutive study visits are missed and the patient is unable to return to the site, the investigator should advise the patient to have protocol-specified safety labs completed at a local laboratory to assess for any safety concerns. In both cases, the local laboratory results should be documented in the eCRF.
- Investigational sites should report all serious adverse events, adverse events of clinical interest, overdose, and pregnancy that the patient reports during these calls within 24 hours of awareness.
- Patients should be reminded of the importance of taking study drug daily or of using back-up contraception if study drug is interrupted.
- Study patients should continue to complete their daily eDiary, even if they run out of study drug, and site staff should motivate them to do so.

Patients should have the contact details of the investigational site medical staff to report any medical issues, including adverse events they may experience in real time.

As soon as the study patients are able to return to the investigational site for an on-site visit, they should do so. The next scheduled visit should occur on the target date as per the Schedule of Activities (see Table 1).

Study Participant Study Drug Supply

If a regional lockdown, travel restrictions, or site closure is imminent due to the COVID-19 pandemic, sites are encouraged to dispense additional study drug at an expected study visit or request patients to return for an unscheduled visit for additional study drug dispensation so patients have sufficient supply until their next upcoming visit. Patients should be instructed to contact the site to report any medical issues they may experience and site staff should communicate with the patients to determine if it is appropriate for the patient to continue dosing with study drug if/when in-person study visits are not possible.

For cases where study patients are unable to visit the investigational site to pick up study drug, a direct-to-patient delivery of study drug by site staff or shipment via contracted courier may be possible. Consent authorizing direct-to-patient supply will be obtained. Sites should defer to national guidance on how this will occur. Where permitted by national guidance, verbal consent will be taken via telephone or video call and noted in the patient's source file. Where required, by national guidance, this will be followed up with written consent during the next clinic visit. Every effort will be made to obtain the patient's written consent for direct-to-patient delivery prior to delivery or shipment, where this is required by national guidance.

In the event that none of the above are possible for participants to continue taking study medication, a patient may need to be discontinued per the study protocol. Such decisions will be made on a case-by-case basis in discussion with the investigator and medical monitor.

On-Site Study Monitoring Restrictions

In the event study monitors/clinical research associates are not allowed to travel and/or return to a clinical site to monitor and source document verify study data, Myovant has developed plans to ensure monitors:

- Remotely verify source documentation as much data as reasonably possible without burdening sites, if allowed by the study site and country regulations, focusing on pages key to the interpretability of the study and the safety of participants.
- Remotely monitor study data through cross checking of various systems housing patient data against what is captured in the eCRFs.

Additional guidance on conducting clinical trials during the COVID-19 pandemic may be found in the following documents released by Regional Health Authorities, which may be updated (updates supersede the versions listed here):

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated 27 Jan 2021);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic – Version 4 04 Feb 2021.

APPENDIX 9. ABBREVIATIONS

List of Abbreviations and Definition of Terms

Abbreviation	Definition
β-hCG	beta human chorionic gonadotropin
AGC	atypical glandular cell
AGUS	atypical glandular cells of undetermined significance
AIS	adenocarcinoma in situ
ALT	alanine aminotransferase
ASC-H	atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
ATE	arterial thrombotic or thromboembolic event
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CKD	chronic kidney disease
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	novel coronavirus 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DXA	dual-energy X-ray absorptiometry
E2	estradiol
ECD	estimated conception date
eCRF	electronic case report form
EDD	estimated date of delivery
eDiary	electronic diary
EHP-30	Endometriosis Health Profile-30
EOT	end-of-treatment
ET	early termination
FDA	Food and Drug Administration
FDC	fixed-dose combination (tablet)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	interactive web-response system
KM	Kaplan Meier
LH	luteinizing hormone
LSIL	low-grade squamous intraepithelial lesion
MBL	menstrual blood loss
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified ITT
NETA	norethindrone acetate
PI	Pearl Index
PTFU	post-treatment follow-up
PTH	parathyroid hormone
QD	once daily
QTcF	QTc corrected using Fridericia's formula
rITT	restricted intent-to-treat
STD	sexually transmitted disease
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

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Clinical Study Protocol

Protocol Title:	A Phase 3, Single-Arm, Open-Label Study to Evaluate the Contraceptive Efficacy of Relugolix Combination Therapy in Healthy Women 18 to 35 Years of Age Who are at Risk for Pregnancy
Protocol Number:	MVT-601-050
Amendment Number:	1
Compound:	Relugolix Combination Therapy (relugolix, estradiol, norethindrone acetate)
Study Phase:	Phase 3
Short Title:	A Phase 3 Contraceptive Efficacy Study of Relugolix Combination Therapy in Healthy Women Who are at Risk for Pregnancy
Sponsor Name:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Agency Identifier Numbers:	IND 131161
Approval Date:	Original: 12 AUG 2020 Amendment 1: 21 Dec 2020

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

A Phase 3, Single-Arm, Open-Label Study to Evaluate the Contraceptive Efficacy of Relugolix Combination Therapy in Healthy Women 18 to 35 Years of Age Who are at Risk for Pregnancy

Protocol Number: MVT-601-050 Amendment 1

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

DocuSigned by:

[redacted]

20-Dec-2020 | 4:47 PM PST

Date

18-Dec-2020 | 2:22 PM PST

Date

20-Dec-2020 | 8:51 AM PST

Date

18-Dec-2020 | 2:29 PM PST

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)	Principal Investigator Signature
Clinical Site	Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Single-Arm, Open-Label Study to Evaluate the Contraceptive Efficacy of Relugolix Combination Therapy in Healthy Women 18 to 35 Years of Age Who Are at Risk for Pregnancy

Short Title: A Phase 3 Contraceptive Efficacy Study of Relugolix Combination Therapy in Healthy Women Who Are at Risk for Pregnancy

Protocol Number: MVT-601-050

Location: United States (US)

Study Centers: Approximately 40 sites

Study Phase: Phase 3

Target Population: Women 18 to 35 years of age who are at risk for pregnancy

Rationale:

This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy. Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis. Both conditions are prevalent in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy of relugolix combination therapy in treatment of symptoms associated with endometriosis or uterine fibroids, or the safety of patients undergoing treatment with relugolix combination therapy. By quantifying the contraceptive effectiveness of relugolix combination therapy (using the Pearl Index [PI]), results from this study will provide evidence for patients and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception while being treated with relugolix combination therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times \text{(number of on-treatment pregnancies)}}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

Overall Design:

Study MVT-601-050 is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy (relugolix 40 mg, estradiol [E2] 1 mg, and norethindrone acetate [NETA] 0.5 mg). Approximately 900 sexually active, healthy women 18 to 35 years of age who will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

The study consists of a Screening Period (Visit 1), a 52-week Treatment Period (Visits 2 to 6), and a 14-day Follow-Up Period (Visit 7).

Participant eligibility will be determined based on assessments performed at Visit 1, when the participant's medical and gynecological history (including contraception and use of prior medications) will be reviewed; their height, weight, and vital signs will be measured; and physical, gynecological, and breast examinations will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy, and participants will be screened for the sexually transmitted diseases (STDs) gonorrhea and chlamydia. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening.

Participants who meet all eligibility criteria will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Prior to initiation of treatment with relugolix combination therapy on Day 1 (Visit 2), continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. Participants must have a negative urine pregnancy test. Participants will also receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Finally, study medication will be dispensed, together with instructions for administration and back-up contraception, if applicable. The window for initiating dosing with relugolix combination therapy also depends upon contraceptive status. If Visit 2 occurs within the correct window, dosing may begin at Visit 2. Otherwise, the participant will initiate dosing at home when the appropriate window is reached and after another negative urine pregnancy test result is recorded in the eDiary. Thereafter, continuous treatment with relugolix combination therapy will be taken for 13 consecutive 28-day treatment cycles.

Throughout the Treatment Period, compliance with study intervention administration will be recorded daily in the eDiary. At the completion of each 28-day treatment cycle, the participant will record the results of a urine pregnancy test and indicate whether intercourse or use of additional contraception occurred during the previous 28-day treatment cycle. Each treatment cycle starts with the result of a home pregnancy test, the result of which must be negative and must be entered in the eDiary for a participant to continue in the study. Assessments of safety (physical, gynecological, and breast examinations; laboratory assessments; vital signs; etc.) will be performed throughout the study. Telephone visits to assess compliance and safety will be performed approximately 6 weeks following each on-site visit during the treatment period.

Fourteen days after discontinuation of treatment, a follow-up/EOT visit (Visit 7) will be conducted. All assessments done at on-treatment visits will be repeated and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for selected serum chemistry assessments, including β-hCG to determine pregnancy and safety assessments will be performed. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

Any participant who becomes pregnant during the study or is pregnant at the follow-up visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Inclusion and Exclusion Criteria:

Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 35 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
6. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through the end of study participation;
7. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
8. Has body mass index (BMI) ≥ 18 kg/m^2;
9. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of VTE due to prolonged immobilization (eg, due to trauma, surgery, or other illness markedly limiting mobility) within 2 weeks prior to screening; plans for surgery requiring prolonged immobilization during the study; has a hereditary or acquired

predisposition to or elevated risk for venous or arterial thrombosis, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant); or has thrombogenic cardiac valve or rhythm abnormalities of the heart associated with thromboembolism (eg, atrial fibrillation);

Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end-organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

Note: The specific reasons for exclusion should be documented in the eCRF.

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (AST, ALT, total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

11. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
    d. High-density lipoprotein level < 50 mg/dL.
12. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

13. Has a known history of infertility or sub-fertility;
14. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
15. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening, (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.
16. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, bleeding from uterine fibroids or a cervical polyp, recurrent bleeding after intercourse);
17. Has a known submucosal fibroid.

Other Conditions/Disorders

18. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
19. Has known HIV infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
20. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;

21. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants 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 or mental health professional's judgement, 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;
22. Has any disease that may worsen under hormonal treatment, such as known gall bladder disease or a hepatic hemangioma;
23. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
24. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
25. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

26. Has a known or suspected pregnancy;
27. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
28. Is breastfeeding;

    Note: If recently stopped breastfeeding, must have resumed menstruation and must have had at least two normal menstrual cycles.

Concomitant and Recent Medications/Devices

29. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
30. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
31. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein).

Miscellaneous

32. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

Disclosure Statement: This is a single-arm, open-label study to evaluate the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy.

Number of Participants:

Approximately 1060 participants will be screened to achieve approximately 900 participants enrolled to study intervention. The sample size has been set to attain at least 5,000 treatment cycles at-risk for pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse) in participants 18 to 35 years of age at the time of enrollment (see Section 9.2). Sample size reassessment will be performed periodically to check the key assumptions used for sample size calculations. If the interim data shows that the observed PI is likely greater than the expected PI (ie, PI = 2), the planned sample size of 900 participants will be reassessed and increased.

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study but do not participate in the study are not considered enrolled.

Intervention Groups and Duration:

Relugolix combination therapy (relugolix 40 mg, E2 1 mg, and NETA 0.5 mg) as a fixed-dose combination tablet is to be taken orally QD at approximately the same time each day, 1 hour before or 2 hours after a meal. Relugolix combination therapy is continuous; that is, a tablet is to be taken daily for the entire duration of the treatment period, without a drug-free interval.

Study intervention will be self-administered during 13 consecutive 28-day treatment periods ("Cycles"), for a total duration of 52 weeks.

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

Participants may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove participants from therapy under this protocol for reasons of safety and/or lack of compliance, as discussed below. Participants removed from study intervention for any reason will, if possible, undergo assessments for an early discontinuation visit (see Schedule of Activities, Section 1.3) approximately 14 days after the end of treatment (ie, after the participant's last dose of study intervention).

Criteria for Evaluation:

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the estimated date of delivery (EDD) will be ascertained. The estimated conception date (ECD) will be calculated as:

- EDD − 38 weeks = ECD

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses, or β-hCG level.

Statistical Methods:

Contraceptive Efficacy

This study has one primary endpoint, the At-Risk PI, calculated on the basis of the number of on-treatment pregnancies in the numerator and the number of at-risk cycles of exposure in the denominator. The numerator and denominator are thus slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, the primary contraceptive efficacy analysis, will be conducted using an restricted intent-to-treat (rITT) population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred (ie, a treatment cycle containing an ECD for a pregnancy). The At-Risk PI will be presented together with the two-sided 95% confidence interval (CI) calculated based on a Poisson distribution (Benda et al. 2004). There is no hypothesis associated with the primary endpoint.

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution.

Safety

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention, and severity. An adverse event reported more than once for a participant will be counted once at the maximum severity or strongest relationship to study intervention when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

Sample Size Determination

Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 5,000 treatment cycles at-risk for pregnancy in participants 18 to 35 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of thirteen 28-day treatment cycles;
- 45% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 4 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% CI for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$, where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100 woman-years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with the FDA Guidance for Industry (FDA 2019).

With at least 5000 on-treatment cycles at-risk for pregnancy (~ 400 woman-years), the study will have approximately 90% power for the upper bound of the 95% two-sided CI for the PI to be below 5.

Approximately 900 participants must be enrolled to achieve at least 5000 at-risk cycles. With the assumption of a screening failure rate of 15%, a total of approximately 1060 participants will be screened.

The number of at-risk cycles will be monitored, and enrollment will be adjusted to ensure that at least 5000 on-treatment at-risk cycles are achieved at the end of the study.

Sample Size Reassessment

To ensure that the trial is adequately powered for the evaluation of contraceptive efficacy measured by PI, sample size reassessment will be performed periodically to check the key assumptions used for sample size calculations. In particular, the PI will be calculated from interim data to check the accuracy of the assumption (PI = 2) used for the initial sample size calculation. The planned sample size of 900 participants may be adjusted from the interim calculation to ensure the study is adequately powered to evaluate contraceptive efficacy. The detailed methodology for the sample size reassessment during the trial will be described in the statistical analysis plan.

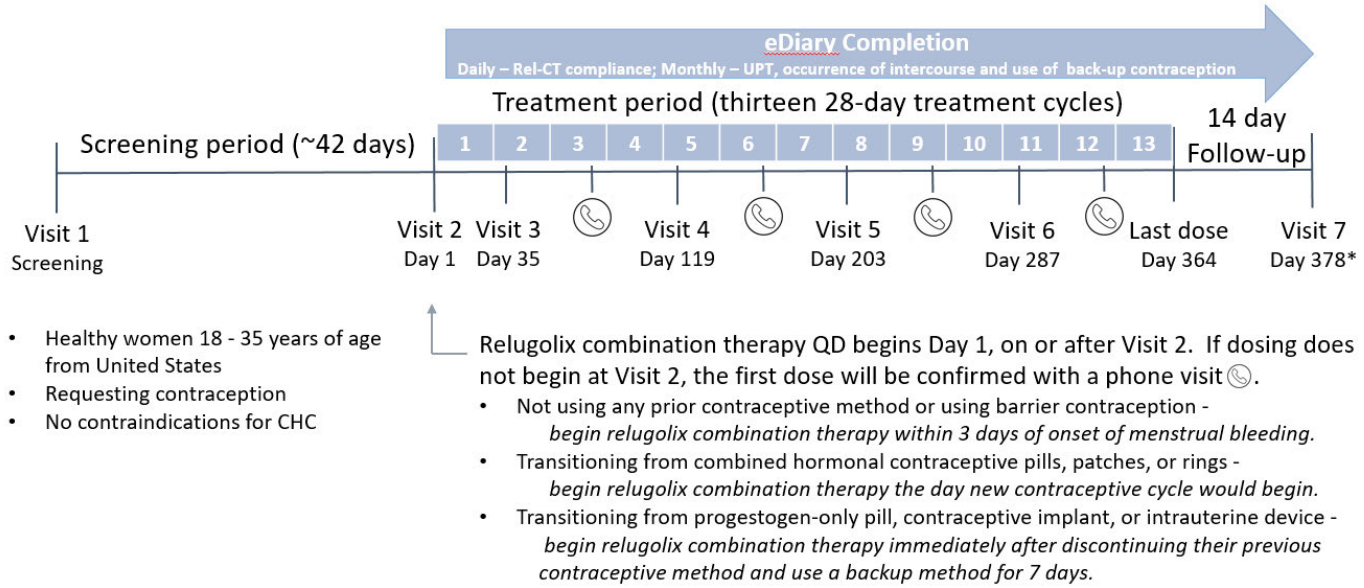
Data Monitoring Committee:

This is an open-label single-arm study, and no Data Monitoring Committee will be convened. The safety of study participants will be closely monitored on an ongoing basis by Myovant Sciences representatives in close consultation with the Drug Safety and Pharmacovigilance Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to investigators.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: MVT-601-050 Study Schematic



Abbreviations: CHC = combined hormonal contraceptive; E2 = estradiol; eDiary = electronic diary; NETA = norethindrone acetate; QD = once daily; Rel-CT = relugolix combination therapy (relugolix 40 mg, E2 1 mg, NETA 0.5 mg); UPT = urine pregnancy test.
* or 14 days after the last dose.
Note: During the treatment period Visits occur approximately 7 days after the end of the previous cycle. Phone visits occur approximately 6 weeks after the subsequent Visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities for MVT-601-050

Trial Period	**Screening**	**Allocation**	**Treatment Period**							
Visit	**V1**	**V2[a]**	**V3**	**P3**	**V4**	**P4**	**V5**	**P5**	**V6**	**P6**
Visit Timing	**−42 D**	**On or prior to D1[b]**	**7 days after Cycle 1**	**~6 wks after V3**	**~7 days after Cycle 4**	**~6 wks after V4**	**7 days after Cycle 7**	**~6 wks after V5**	**7 days after Cycle 10**	**~6 wks after V6**
Day of Study Intervention Treatment[c]		**D 1[d]**	**D 35**	**D 77**	**D 119**	**D 161**	**D 203**	**D 245**	**D 287**	**D 329**
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Gynecological History	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
Contraceptive History	X	X								
Dispense eDiary		X								
eDiary Training/Re-Training[e]		X	X	X	X	X	X	X	X	X
Dispense Study Intervention		X	X		X		X		X	
eDiary Compliance/Data Review			X	X	X	X	X	X	X	X
Drug Accountability[f]			X		X		X		X	
Contraceptive Counseling									X[g]	X[g]
Physical Examination[h,i]	X									
GYN & Breast Examination[i]	X									
Height	X									
Weight, Vital Signs (HR, BP)	X	X	X		X		X		X	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory[j]	X						X			
Gonorrhea/Chlamydia Test	X									
Cervical Cytology[k]	X									
Serum β-hCG[l]	X									
Urine Pregnancy Test[m]		X	X		X		X		X	
Transvaginal ultrasound										

Table 1: Schedule of Activities for MVT-601-050 (Continued)

Trial Period	**Post-Treatment Period**		**Unscheduled**
Visit	**Follow-Up/EOT (V7)[n]**	**Pregnancy**	
Visit Timing	**14 days after Cycle 13 or Last Dose**	**Upon diagnosis**	
Day of Study Intervention Treatment[c]	**D378**	**NA**	**NA**
Informed Consent			
Inclusion/Exclusion Criteria			
Medical History			
Gynecological History			
Prior and Concomitant Medication Review	X	X	X
Contraceptive History			
Dispense eDiary			
eDiary Training/Re-Training[e]			X[p]
Dispense Study Intervention			X[p]
eDiary Compliance/Data Review	X	X	X[p]
Drug Accountability[f]	X	X	X[p,q]
Contraceptive Counseling	X[g]		
Physical Examination[h,i]	X	X	X[p]
GYN & Breast Examination[i]	X	X	X[p]
Height			X[p]
Weight, Vital Signs (HR, BP)	X	X	X[p]
Adverse Event Monitoring	X	X	X
Clinical Laboratory[j]	X	X	X[p]
Gonorrhea/Chlamydia Test			X[p]
Cervical Cytology[k]			X[p]
Serum β-hCG[l]	X	X	X[p]
Urine Pregnancy Test[m]	X		X[p]
Transvaginal ultrasound		X[o]	

Abbreviations: β-hCG = beta human chorionic gonadotropin; AGC = atypical glandular cells; AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; ALT = alanine transaminase; ASC-H = atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; AST = aspartate transaminase; BP = blood pressure; D = day(s); EDD = estimated date of delivery; eDiary = electronic diary; EOT = end-of-treatment; GGT = gamma-glutamyltransferase; GYN gynecologic; HPV = human papilloma virus; HR = heart rate; HSIL = high-grade squamous intraepithelial lesion; LDH = lactic dehydrogenase; LSIL = low-grade squamous intraepithelial lesion; NA= not applicable; P = phone contact; V = visit.

a. The timing of Visit 2 depends on contraceptive status at screening and the need for washout. Visit 2 should occur after screening tests results indicating eligibility are available.

b. Study intervention dosing (Day 1) occurs during the allocation period (Visit 2). The timing of Day 1 may vary based on the following:

- For participants not using any prior contraceptive method or using barrier contraception Day 1 must occur within 3 days of the onset of menses and after a negative urine pregnancy test has been recorded in the participant's eDiary. If Visit 2 occurs within 3 days of the onset of menses, the participant will begin her first treatment cycle of relugolix combination therapy dosing at the study visit. If the visit is not within this window, dosing will begin once the participant reports the onset of the next menses, followed by entry of a negative urine pregnancy test result in the eDiary. The eDiary will then instruct the participant to take and record the first dose of study intervention.
- For participants transitioning from combined hormonal contraceptive pills, patches, or rings: Day 1 is the day she would normally initiate a new contraceptive cycle. If Visit 2 cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.
- For participants transitioning from progestin-only pills: Visit 2/Day 1 must be scheduled the day after completing treatment with the prior method and the participant must use a back-up method for the first 7 days of relugolix combination therapy.
- For participants using a contraceptive implant or intrauterine device: Visit 2/Day 1 must be scheduled the day the implant or device is removed. The participant must use a back-up contraceptive method for the first 7 days of relugolix combination therapy.

c. Visits should be scheduled on the target day of study intervention treatment as indicated. If this this not feasible, the visit should occur as soon after the target day as possible. Treatment must not be extended beyond Day 364.
d. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact.
e. Initial eDiary training to be performed when eDiary is dispensed. eDiary training for the participant should be performed/reinforced throughout the study.
f. The participant should be asked to bring all study intervention to the clinic for each visit (see Section 6.4).
g. Counseling regarding post-trial contraceptive use should be provided to all participants at Visit 6 and repeated at Phone Visit 6 and Visit 7 (Follow-up/EOT).
h. A complete physical exam will be conducted at Visit 1 and Visit 7 and will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All other physical examinations should focus on signs and symptoms reported by the participant.
i. Physical, gynecologic, and breast examinations should be conducted by a licensed health professional (eg, physician, nurse practitioner, physician assistant).
j. Clinical laboratory tests will include hematology, chemistry, lipid profile, and Hemoglobin A1C at screening. The screening sample must be obtained in the fasted state (no food or drink other than water after midnight). If the screening period is extended by more than 6 weeks for any reason, screening laboratories (chemistry and hematology) should be repeated prior to administration of the first dose of study intervention. Assessments at Visits 5 and 7 will be limited to liver tests (ALT/AST/GGT/total bilirubin/alkaline phosphatase/LDH).
k. Cervical smear is only applicable to participants 21 years of age and older (or who will become age 21 during the course of the trial). Cervical cytology does not need to be performed if a normal cervical smear (ie, no evidence of ASCUS with high-risk HPV positive, ASC-H, LSIL, HSIL, squamous cell carcinoma, AGUS, AGC-neoplastic or AIS) performed within 18 months of Visit 1 can be documented and the participant does not report a history of abnormal results within the past 3 years. Cervical smear may be performed by a nurse practitioner or physician's assistant if licensed in the state, is trained, and it is within their scope of practice.
l. A serum β-hCG pregnancy test is required at Visit 1 and Visit 7 (Follow-up/EOT). Serum testing should also be performed during the trial if a pregnancy is suspected, or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound).

m. A urine pregnancy test will be performed at each site visit after screening. Additionally, a home urine pregnancy test performed by the participant is required prior to the start of each cycle and the result must be negative to continue. Any positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound, when applicable).
n. Follow-up/EOT visit also to be done in case of early discontinuation.
o. Transvaginal ultrasonography will be performed to determine gestational age/EDD.
p. For an unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
q. eDiary and any remaining drug should be collected by the site at this visit.

2. INTRODUCTION

Relugolix is a daily, orally active, potent, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) (relugolix combination therapy) for the treatment of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Relugolix competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are considerably reduced, with the reduction in FSH concentrations preventing natural follicular growth and development, limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Further, prevention of an LH surge inhibits ovulation, and therefore the corpus luteum does not develop, which precludes the production and secretion of progesterone into the systemic circulation. Relugolix is combined with E2 1 mg and NETA 0.5 mg to maintain E2 concentrations within a therapeutic range and progesterone/progestin concentrations at low levels, to treat symptoms associated with endometriosis and uterine fibroids while maintaining BMD and preventing vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen.

Relugolix combination therapy is intended to provide an effective and well-tolerated option for the long-term treatment of symptoms associated with endometriosis and uterine fibroids. This study will evaluate the efficacy and safety of relugolix combination therapy as a contraceptive.

2.1. Study Rationale

Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Uterine fibroids and endometriosis are both prevalent conditions in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy or safety of participants undergoing treatment with relugolix combination therapy for the treatment of symptoms associated with endometriosis or uterine fibroids. This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy.

This study is being conducted in women of reproductive age with presumed normal fertility rather than in women with symptomatic uterine fibroids or endometriosis because those conditions may be associated with subfertility, which would confound assessment of the intrinsic contraceptive effectiveness of relugolix combination therapy. By determination of the Pearl Index (PI) for relugolix combination therapy (ie, by quantifying the contraceptive effectiveness), the study will provide evidence for participants and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception during treatment with relugolix combination therapy.

2.2. Background

Replicate, randomized, double-blind, placebo-controlled, 24-week phase 3 studies followed by a long-term open-label extension study were conducted within each indication to support marketing approval.

To support the uterine fibroid indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with heavy menstrual bleeding associated with uterine fibroids. Patients with confirmed uterine fibroids with heavy menstrual bleeding were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (Studies MVT-601-3001 [N = 387] and MVT-601-3002 [N = 381]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3003), designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the uterine fibroid indication.

A statistically greater proportion of women treated with relugolix combination therapy compared to placebo (73.4% vs. 18.9% [$p < 0.0001$] in MVT-601-3001 and 71.2% vs. 14.7%% [$p < 0.0001$] in MVT-601-3002) achieved the primary endpoint of both a menstrual blood loss volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment. Six key secondary endpoints related to menstrual blood loss volume, amenorrhea, change in hemoglobin, pain associated with uterine fibroids as measured by a Numerical Rating Scale, and change in patient-reported distress from heavy bleeding, passing of blood clots, and pelvic pressure as assessed by the validated Bleeding and Pelvic Discomfort scale, and change in uterine volume were also met. Relugolix combination therapy maintained BMD at levels comparable to placebo over 24 weeks and was generally well tolerated. Additionally, the long-term extension study MVT-601-3003 demonstrated durability of treatment effect for up to 52 weeks. The overall safety profile of relugolix combination therapy for up to 52 weeks was consistent with that observed over the first 24 weeks with low incidence of vasomotor symptoms and maintenance of BMD over time.

To support the endometriosis indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 1250 premenopausal women with pain associated with endometriosis. Patients with confirmed endometriosis with moderate to severe pain were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (MVT-601-3101 [N = 628] and MVT-601-3102 [N = 622]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3103) designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the endometriosis indication.

Patients receiving relugolix combination therapy achieved both co-primary endpoints by demonstrating clinically-meaningful pain reductions compared to placebo for dysmenorrhea (74.5% vs. 26.9% [$p < 0.0001$] in MVT-601-3101 and 75.2% vs. 30.4% [$p < 0.0001$] in MVT-601-3102) and for nonmenstrual pelvic pain (58.5% vs. 39.6% [$p < 0.0001$] in MVT-601-3101 and 66% vs. 42.6% [$p < 0.0001$] in MVT-601-3102).

In study MVT-601-3101, all seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, and impact of pain on daily activities as measured by the Endometriosis Health Profile-30 (EHP-30) pain domain, greater proportions of women not using analgesics (p-values < 0.0001), changes in mean nonmenstrual pelvic pain (p = 0.0002), greater proportions of women not using opioids (p = 0.0005), and changes in mean dyspareunia (painful intercourse; p = 0.0149). In study MVT-601-3102, six of seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, impact of pain on daily activities as measured by the EHP-30 pain domain, a greater proportion of women not using opioids (all p-values < 0.0001), changes in nonmenstrual pelvic pain (p = 0.0012), and dyspareunia (painful intercourse; p = 0.0371). Relugolix combination therapy was generally well tolerated with minimal BMD loss over 24 weeks.

In addition, an ovulation inhibition study with relugolix combination therapy in healthy adult premenopausal women has been completed (MVT-601-046, N = 67). This open-label, single-arm study included a pre-treatment period to confirm ovulatory status, an 84-day treatment period to assess the effects of relugolix combination therapy on ovarian activity, and a post-treatment follow-up period to determine time to return of ovulation. Ovulation (as assessed by the Hoogland-Skouby scale [Hoogland and Skouby 1993]) was inhibited for 100% of participants during the entire 84-day treatment period, and ovarian activity, as evidenced by the degree of follicular growth, was markedly suppressed. Pituitary secretion of FSH and LH, and ovarian production of estradiol and progesterone were markedly suppressed with relugolix combination therapy, with median E2 serum concentrations consistently maintained within an approximate range of 30 to 40 pg/mL during the 84-day treatment period. Mean progesterone concentrations were consistently maintained between 0.94 and 1.25 nmol/L, with individual values all below 5 nmol/L, the cut-off value for luteal activity in the Hoogland-Skouby assessment scale, consistent with the suppression of ovulation observed across all three treatment periods. Additionally, endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness consistently maintained between 4 and 5 mm and likely contributing to the reduction in overall bleeding. All women returned to ovulation or began menses upon discontinuation of relugolix combination therapy demonstrating the revisability of the treatment effect. The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days, with 97.01% (65 of 67 participants) having a confirmed ovulation within 36 days post treatment (one participant ovulated on Day 43 and the other began menstruation on Day 39).

As of January 2020, the relugolix clinical development program includes data from 3258 participants and patients exposed to relugolix either as monotherapy or as relugolix combination therapy. These data include single doses up to 360 mg and multiple doses up to 120 mg administered for more than a year. Data from the pivotal phase 3 studies in the uterine fibroid indication demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. Data from the pivotal phase 3 studies in the endometriosis indication also demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. These collective data continue to support a favorable benefit/risk profile for the proposed indications. By the time this contraception study is completed, it is expected that over 1500 participants and patients will have received relugolix combination therapy, with over 500 participants and patients having received relugolix combination therapy for 1 year and over 200 participants and patients for up to 2 years.

In summary, data from the relugolix nonclinical, pharmacodynamic, and clinical development program support the proposed mechanism of action for relugolix combination therapy, which works through inhibition of follicular development and prevention of ovulation, suppressing the secretion of endogenous estradiol and progesterone. Data from the completed pivotal phase 3 studies demonstrate robust efficacy results for the indications studied. Data from the ovulation inhibition study demonstrate maximal suppression of ovulation. The currently available safety database is large and allows characterization of the safety profiles of relugolix monotherapy and relugolix combination therapy to support initiation of this study. A detailed description of the chemistry, pharmacology, efficacy, and safety of relugolix is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of relugolix combination therapy may be found in the current Investigator's Brochure.

2.3.1. Risk Assessment

On the basis of nonclinical studies, clinical safety analyses, and data available for investigations of similar compounds, relugolix combination therapy may be associated with potential risks. The risk assessment and mitigation strategies for this protocol are outlined in Table 2.

Table 2: Study MVT-601-050: Risk Assessment and Mitigation Strategies

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Identified Risk		
Uterine fibroid prolapse or expulsion.	Exclusion of participants with abnormal bleeding due to uterine fibroids or known submucosal uterine fibroids.	Active monitoring of adverse events.
Potential Risk		
Hepatic Transaminase Elevation Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver biochemical tests are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 × ULN; total bilirubin values > 1.5 × ULN.	Hepatic transaminases are monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009) in all relugolix studies. Abnormal liver tests (AST or ALT > 3 × ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.
Embolic and Thrombotic Events Oral contraceptives and hormone replacement therapy are associated with an increased risk for a venous or arterial thromboembolic event.	Exclusion of participants with previous or current venous thromboembolism.	Active monitoring of adverse events.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Embryofetal Toxicity In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures similar to those at the recommended human dose. No effects on embryofetal development were observed in rats in a similar study. In both rabbits and rats, no fetal malformations were present at any dose level tested that were associated with relugolix exposures similar to and approximately 733-times the exposures in women at the recommended human dose, respectively. Based on these findings, exposure to relugolix combination therapy early in the first trimester of pregnancy has the potential to increase the risk of early pregnancy loss.	Exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.
Tumors (Breast and Liver) Breast cancer is a hormonally sensitive tumor. There is substantial evidence that combined oral contraceptives do not increase the incidence of breast cancer. Although past studies have suggested that combined oral contraceptives might increase the incidence of breast cancer, more recent studies have not confirmed such findings. Hepatic adenomas are associated with hormonal contraceptive use and a long-term increased risk of developing hepatocellular carcinoma.	Exclusion criteria for participants with known, suspected, or a history of breast cancer or active liver disease.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase. Active monitoring of adverse events.

Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Mood Disorders Depression has been reported with the prescribed use of GnRH receptor antagonists and agonists and with combined oral contraceptives and hormone replacement therapy.	Exclusion of participants whose mood disorder has been unstable or not well controlled. Exclusion of participants who have major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria.	Active monitoring of adverse events.
Gallbladder Disease Combined hormonal therapy use may be associated with gallbladder disease.	Exclusion criteria for ALT and AST > 2 × ULN; total bilirubin values > 1.5 × ULN.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase and adverse events is performed during the study.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; GnRH = gonadotropin-releasing hormone; ULN = upper limit of normal.

Adverse drug reactions associated with relugolix combination therapy in women with uterine fibroids include the nonserious adverse events of hot flush, abdominal pain, uterine bleeding, alopecia, libido decreased, irritability, hyperhidrosis, dyspepsia, and breast cyst and serious adverse events of uterine myoma prolapse and expulsion. Refer to the Investigator's Brochure for information on adverse events observed in the endometriosis program for relugolix combination therapy.

In completed phase 1, 2, and 3 studies, there were no drug-specific trends observed in mean or individual patient vital sign measurements, laboratory test results, or electrocardiogram parameters, with the exception of infrequent transient and predominantly mild hepatic transaminase elevations that were observed at a frequency comparable to that in placebo.

No new safety concerns have been identified during active ongoing monitoring.

Overall, the benefit/risk profile remains favorable for the continued development of relugolix combination therapy.

2.3.2. Benefit Assessment

Relugolix combination therapy is a once daily oral medication that has been shown to achieve 100% suppression of ovulation in an ovulation inhibition study (MVT-601-046), suggesting that with appropriate use it has the potential to be a highly effective contraceptive method. Additionally, prompt resumption of ovulation following discontinuation of relugolix combination therapy was observed, indicating the return to fertility is rapid and predictable.

The contraceptive action of relugolix combination therapy is mediated by relugolix, which suppresses follicular development and endogenous production of estrogen and progesterone. The risks of bone loss and vasomotor symptoms associated with a hypoestrogenic state, as well as endometrial hyperplasia from unopposed estrogen, are mitigated by administering relugolix in combination with E2 and NETA at low doses commonly used for hormone replacement therapy in menopause rather than the higher doses used in combined hormonal contraceptives to suppress ovulation. The low dosing of E2 and NETA in relugolix combination therapy may be considered an advantage to those who prefer to minimize the use of exogenous hormones.

Similar to continuous or extended cycle oral contraceptive regimens, relugolix combination therapy may benefit women who wish to limit cyclic bleeding for personal reasons. In the uterine fibroid studies, relugolix combination therapy was associated with an 84.3% reduction in menstrual blood loss volume and a high proportion of patients achieved amenorrhea (52.3% in MVT-601-3001 and 50.4% in MVT-601-3002). This change in the menstrual bleeding pattern may be considered as an advantage to some women.

Relugolix combination therapy has been generally well tolerated in most patients and participants, with an overall low rate of discontinuation due to adverse events.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with relugolix combination therapy are justified by the anticipated benefits that may be afforded to participants in this study who seek effective contraception.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 3.

Table 3: Study MVT-601-050 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.

Objectives	Endpoints
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

4. STUDY DESIGN

4.1. Overall Design

This is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy. Approximately 900 sexually active, healthy women 18 to 35 years of age who will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy. To ensure the study is adequately powered for the assessment of the primary endpoint of the study, the PI, sample size reassessment will be performed periodically to assess the study power by evaluating the key assumptions used to determine whether the planned sample size of 900 participants needs to be adjusted based on the interim review of the trial data (see Section 9.2.3).

After participants sign the informed consent form (ICF), their eligibility will be assessed at Screening/Visit 1 (see Schedule of Activities; Table 1). After a thorough review of the participant's medical history, gynecological history including contraception, and use of prior medications, their height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial), if no normal result is available from an examination within 18 months prior to screening. Screening tests for the sexually transmitted diseases (STD) gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible for rescreening once they have received adequate treatment for the identified STD (see Section 8.1.2).

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of

the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. Home pregnancy tests will be provided for assessment prior to each cycle as required by the study and as needed during the cycle.

If Visit 2 occurs within 3 days of the onset of menses for participants not using any contraceptive method or using barrier contraception, or within the appropriate window for participants transitioning from another contraceptive method, the participant will begin her first treatment cycle of relugolix combination therapy by dosing with study medication at Visit 2. If the visit is not within the window to begin dosing, the participant will be dispensed the study intervention for initiation at home. When the participant reports the onset of the next menses in the eDiary or reaches the appropriate window to begin dosing if transitioning from another contraceptive method, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention. The first dose of study intervention will be confirmed by a phone visit. Once dosing of study intervention begins, the eDiary is organized by 28-day treatment cycles (ie, Cycle 1, 2, 3….), which are successive periods of 28 consecutive days. The eDiary continues with daily questions related to the intake of study intervention. At the end of each 28-day treatment cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding treatment cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding treatment cycle. Each subsequent treatment cycle starts with the result of a home pregnancy test, which must be negative and must be entered in the eDiary for a participant to continue in the study.

Participants will return to the clinic in the first week after completion of Cycle 1 for Visit 3. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Other records in the eDiary will be assessed, including use of other forms of contraception, occurrence of sexual intercourse during the first cycle (recorded once, at the end of the cycle), results of home pregnancy tests (if applicable), and the result of the protocol-required home pregnancy test prior to the start of Cycle 2. The occurrence of adverse events and use of concomitant medication since the last visit will be assessed. Body weight and vital signs will be measured. Study medication will be dispensed. Approximately 6 weeks after Visit 3, a telephone contact will be made (Phone 3; see Table 1), focusing on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable.

On-treatment site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur in the first week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Approximately 6 weeks following each on-treatment site visit, the participant will be contacted by telephone (Phone 4, Phone 5, and Phone 6). The site visits will have the same assessments described for Visit 3 above. Blood samples for liver tests will be collected at site Visit 5. The telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last on-treatment visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

Fourteen days after completion of Cycle 13, or after early discontinuation of treatment, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on-treatment visits will be repeated, and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted, and blood samples will be obtained for liver tests and β-hCG to determine pregnancy. Post-treatment contraception will be discussed and any remaining study medication and the eDiary will be collected.

Any participant who becomes pregnant during the study or is pregnant at the follow-up/EOT visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

4.2. Scientific Rationale for Study Design

This is an open-label, single-arm, phase 3 study designed to demonstrate the contraceptive efficacy of relugolix combination therapy. The primary objective is to assess the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy, as expressed by the At-Risk PI in the restricted intent-to-treat (rITT) population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse. Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles") for a total duration of 52 weeks.

To demonstrate the intrinsic contraceptive efficacy of relugolix combination therapy, a study population of women without impaired fertility is considered adequate (ie, women without gynecological conditions such as endometriosis or uterine fibroids, who have regular menstrual cycles, and who are in the optimum age range for conception [ie, between 18 to 35 years of age]). To support a proper assessment, women participating in this study should be sexually active with men and should agree to abstain from using other forms of contraception during the study.

Participants will visit the study site approximately every 12 weeks for safety evaluations, which include review of adverse events, eDiary, and concomitant medications, and collection of weight, vital signs (blood pressure, heart rate), and urine pregnancy test. Clinical laboratory evaluations will occur at Visit 5 and 7. The study eligibility criteria were designed to minimize risk to participants and rules for evaluation of liver test abnormalities, consistent with FDA guidance (FDA 2009), have been incorporated into the protocol.

4.3. Justification for Dose

The relugolix combination therapy doses of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg were selected for this study as they are the proposed clinical doses in women with heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

In replicate pivotal phase 3 trials, within each of the indications studied, a 40-mg dose of relugolix combined with E2 1 mg and NETA 0.5 mg resulted in marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women and a decrease in pelvic pain associated with endometriosis, respectively. Across the development programs, the combination of relugolix with E2 and NETA at the selected doses demonstrated maintenance of BMD and prevented vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen. Across all studies, relugolix combination therapy

was generally well tolerated in most participants, with an overall low rate of discontinuation due to adverse events. On the basis of the favorable benefit-risk profile observed in each indication, Myovant intends to commercialize relugolix combination therapy for the treatment of heavy menstrual bleeding associated with uterine fibroids and for pain associated with endometriosis.

In a study evaluating the effects of relugolix combination therapy on ovarian activity in healthy premenopausal women (MVT-601-046), relugolix combination therapy demonstrated inhibition of ovulation, as determined by Hoogland-Skouby score, in 100% of women receiving relugolix combination therapy during the entire 84-day treatment period. Therefore, these same doses are expected to be effective in preventing pregnancy.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed 13 28-day treatment cycles and the follow-up/end-of-treatment (EOT) visit (Visit 7), as shown in the Schedule of Activities (see Table 1).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 35 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
6. Is willing to use the study intervention as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through the end of study participation;
7. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
8. Has body mass index (BMI) $\geq$ 18 kg/m^2;
9. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

5.2. Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of VTE due to prolonged immobilization (eg, due to trauma, surgery, or other illness markedly limiting mobility) within 2 weeks prior to screening; plans for surgery requiring prolonged immobilization during the study; has a hereditary or acquired predisposition to or elevated risk for venous or arterial thrombosis, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant); or has thrombogenic cardiac valve or rhythm abnormalities of the heart associated with thromboembolism (eg, atrial fibrillation);

   Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.
3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end-organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

Note: The specific reasons for exclusion should be documented in the eCRF.

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;

10. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (AST, ALT, total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

11. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
    d. High-density lipoprotein level < 50 mg/dL.
12. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

13. Has a known history of infertility or sub-fertility;
14. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
15. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening, (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.
16. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, bleeding associated with uterine fibroids or a cervical polyp, recurrent bleeding after intercourse);
17. Has a known submucosal fibroid.

Other Conditions/Disorders

18. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
19. Has known HIV infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
20. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
21. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants 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 or mental health professional's judgement, 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;
22. Has any disease that may worsen under hormonal treatment, such as known gall bladder disease or a hepatic hemangioma;
23. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the study intervention or its excipients;
24. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
25. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

26. Has a known or suspected pregnancy;
27. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
28. Is breastfeeding;

    Note: If recently stopped breastfeeding, must have resumed menstruation and must have had at least two normal menstrual cycles.

Concomitant and Recent Medications/Devices

29. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
30. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;

31. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein).

Miscellaneous

32. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

5.3. Lifestyle Considerations

No restrictions are required for treatment with relugolix combination therapy.

5.4. Screen Failures

Participants who consent to participate in the clinical study but are not subsequently entered in the study are considered to have had a screen failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any serious adverse event.

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Note: the study intervention in this study is relugolix combination therapy, also referred to as either relugolix combination therapy or study drug.

6.1. Study Intervention(s) Administered

Fixed-dose combination (FDC) tablets, each consisting of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg will be supplied as immediate-release, yellow, film-coated tablets. In addition to the three active pharmaceutical ingredients, the core tablet formulation consists of compendial grade excipients including mannitol, lactose monohydrate, sodium starch glycolate, hydroxypropyl cellulose, and magnesium stearate.

The study intervention is presented in Table 4.

Table 4: Study MVT-601-050 Study Intervention

Intervention Name	**Relugolix Combination Therapy**
Type	Drug
Dose Formulation	Round film-coated yellow tablet
Unit Dose Strength	FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg)
Dosage Level(s)	Single FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg) QD
Route of Administration	Oral

Use	Experimental
IMP/NIMP	IMP
Sourcing	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee
Packaging and Labeling	Study intervention will be provided in a blister or bottle. Each will be labeled as required per US requirements.

Abbreviations: E2 = estradiol; FDC= fixed-dose combination; IMP = investigational medicinal product; NETA = norethindrone acetate; NIMP = non-investigational medicinal product; QD = once daily; US = United States.

6.2. Preparation/Handling/Storage/Accountability

Relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablets are supplied to the study site in a container with 28 tablets. The FDC tablets are packed in either blisters cards or in a high-density polyethylene bottle. The FDC tablets should be stored in the original closed blister or bottle.

All study participants will take study intervention comprising one tablet daily at approximately the same time, 1 hour before or 2 hours after a meal.

If a dose is missed, instructions are as follows:

- If a dose is missed and the error is recognized on the same calendar day, the study intervention should be taken as soon as possible, and then regular dosing should be resumed the next calendar day at the usual time.
- If the missed dose is not recognized until the next calendar day (one missed dose), the dose intended for that calendar day should be taken as soon as possible, and regular dosing should be resumed the following day at the usual time.
- If 2 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time.
- If 3 to 6 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time. Back-up contraception should be used for 7 days.
- If 7 or more consecutive days are missed, the participant should begin using back-up contraception immediately and should be seen for an unscheduled visit. The medical monitor should be contacted.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. Although participants and investigators are not blinded to the study treatment or the study outcome (pregnancy), bias is limited because the diagnosis of pregnancy is an objective measure.

6.4. Study Intervention Compliance

Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles"), for a total duration of 52 weeks (364 days). Participants should complete their eDiary each day on study and should bring all remaining study intervention and all used study intervention packages to each study visit. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for dose interruptions will also be recorded in the eCRF.

6.5. Concomitant Therapy

Concomitant or prior therapies must be recorded including:

- Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) from signing the ICF through the end of the study; or
- Any vaccine, immunization, or hormonal contraceptive method from 6 months prior to signing the ICF through the end of the study;

This information must be recorded in the following ways:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Medications

Table 5 provides examples of prohibited drug categories and windows of exclusion prior to screening; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding participant use of a particular drug or drug class.

Table 5: Study MVT-601-050 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class and Effect	Examples	Window/Comments
P-glycoprotein Inhibitors and/or Moderate or Strong CYP3A Inhibitors	amiodarone azithromycin[a] carvedilol[d] clarithromycin[a] cobicistat cyclosporine[b] dronedarone erythromycin[a] gentamicin glecaprevir/pibrentasvir indinavir itraconazole ketoconazole lapatinib propafenone quinidine ranolazine ritonavir sofosbuvir/velpatasvir/voxilaprevir tetracycline verapamil[c] vemurafenib	14 days or 5 times the elimination half-life, whichever is longer. (6 months for amiodarone) For participants requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study intervention administration during this period.
Combined P-glycoprotein and Strong CYP3A Inducers	carbamazepine lumacaftor mitotane phenobarbital phenytoin rifampin rifapentine St. John's wort	28 days
Hormonal Contraceptive pills, patches, and vaginal rings	combined or progestin-only Nuva Ring®	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3
Long-acting injectable hormonal contraceptives	depot medroxyprogesterone acetate	9 months
Progestin implants and intrauterine devices	Nexplanon Mirena Paragard	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3

Drug Class and Effect	Examples	Window/Comments
GnRH Antagonists/Agonists	leuprolide acetate injection, such as leuprorelin or goserelin acetate injections elagolix	3 months (6 months for 3-month injections)
Anti-Androgens	danazol	4 months
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3]; 6 months for depot subcutaneous or intramuscular injections)
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene asofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months

Abbreviation: GnRH = gonadotropin-releasing hormone.
a. Roxithromycin is allowed.
b. Tacrolimus is allowed.
c. Amlodipine felodipine, and nifedipine are allowed.
d. Metoprolol and atenolol are permitted.

6.6. Dose Modification

The dose level of relugolix combination therapy cannot be modified because it is administered as a single daily tablet.

Participants 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. Back-up contraception should be advised, as appropriate. Participants may subsequently be re-started on study intervention with the written approval of the sponsor (or designee).

6.7. Intervention After the End of the Study

Not applicable to study MVT-601-050.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Any adverse event that is intolerable to the participant 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 participant if dosing continued;
- If it is discovered after enrollment that a participant failed to meet protocol entry criteria and continued participation would pose an unacceptable risk to their health;
- If the following liver test abnormalities develop, study intervention should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until their laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 × ULN; or
  - ALT or AST > 5 × ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QTc corrected using Fridericia's formula (QTcF) prolongation of more than 500 msec on an electrocardiogram done as part of patient care outside of the study protocol;
- Participants who are, in the opinion of the investigator or medical monitor, grossly noncompliant with the protocol requirements. Gross noncompliance includes < 75% compliance with the study intervention over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive visits) with < 50% of the required number of eDiary entries. Investigators will follow-up with the participant to encourage compliance with study intervention or eDiary prior to discontinuing her from the study;
- If the participant becomes pregnant at any time after signing the ICF, she must be withdrawn immediately (see Section 8.3.5 for information on pregnancy reporting).

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral,

compliance, or administrative reasons. This is expected to be uncommon. The medical monitor should be consulted in advance of withdrawal whenever possible.

- At the time of discontinuing from the study, an EOT visit should be conducted, if possible. See the Schedule of Activities (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1). Guidelines to address study conduct related to restrictions arising from the novel coronavirus 2019 global pandemic are addressed in Appendix 6.

8.1. Efficacy Assessments

8.1.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time point as described in the Schedule of Activities (see Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1.2. Screening Period

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, cervical cancer screening) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (see Table 1).

Prior to conducting any screening procedures, participants will be given a full description of the nature and purpose of the study and will be required to provide written informed consent. The investigator or a designated, medically qualified member of the site staff will interview potential participants and establish their eligibility for inclusion. Potential participants will be screened according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively).

The participant's medical history, gynecological history including contraception, and use of prior medications will be reviewed. Menstrual history will be assessed to ensure the participant has a history of regular menstrual cycles every 21 to 35 days when not using hormonal contraception. If the menstrual cycle duration observed during the screening period does not meet eligibility criteria, screening may be extended with approval of the medical monitor. The participant's height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including β-hCG to rule out pregnancy. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening tests for the STDs gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible to continue screening once they have received adequate treatment for the identified sexually transmitted disease and if the investigator determines the participant is not at high risk for reinfection (eg, because of multiple sex partners or an untreated partner). If the screening period is extended by more than 6 weeks for any reason, screening laboratories (chemistry and hematology) should be repeated prior to administration of the first dose of study intervention.

8.1.2.1. Rescreening

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

8.1.2.2. 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. Other procedures, including cervical cytology, can be retested once without the permission of the medical monitor if necessary due to technical or logistical issues, such as an inadequate sample. Further retesting or retesting for other reasons requires the approval of the medical monitor.

8.1.3. Treatment Allocation

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 2, the timing of which depends on contraceptive status at screening. All use of contraceptives must be discontinued prior to Visit 2.

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an eDiary, which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. The first dose of study intervention will be administered on site at the time of Visit 2 or at home as described below. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact. Home pregnancy tests will be provided for assessment prior to each 28-day treatment cycle as required by the study and as needed during the cycle.

8.1.3.1. Prior Use of Hormonal Contraception, Implants, or Devices

For participants with prior use of hormonal contraception or implantable devices, the first dose of study intervention will be administered at Visit 2.

If the participant is transitioning from combined hormonal contraceptive pills, patches, or rings, she may schedule Visit 2 on the day she would normally initiate a new contraceptive cycle. If the visit cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

If the participant is transitioning from progestin-only pills she must schedule Visit 2 the day after completing treatment and use a back-up method for the first 7 days of relugolix combination therapy.

If the participant is transitioning from a contraceptive implant or intrauterine device, she must schedule Visit 2 the day the implant or device is removed and use a back-up method for the first 7 days of relugolix combination therapy. Note that only participants who have requested removal of their implant or intrauterine device for reasons unrelated to the purpose of enrollment may be considered for participation.

Participants using long-acting injectable contraceptive methods are not eligible to screen for the study until 9 months following their last dose.

8.1.3.2. No Prior Contraceptive Use or Use of Barrier Methods

If the participant was not using any prior contraceptive method or was using barrier contraception (diaphragm, cervical cap, male condom, female condom, or spermicidal foam, sponges, and film), she may schedule Visit 2 within 3 days of the onset of menses and the first dose of study intervention will be administered the day of the visit. If the visit cannot be reliably scheduled within the window to begin dosing, the visit should be scheduled prior to the onset of menses. Visit 2 procedures will be conducted, and the participant will begin daily eDiary entries related to the onset of menses. When the participant reports the onset of the next menses in the eDiary, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

8.1.4. Treatment Period

Once dosing of study intervention has been initiated, participants will take their study intervention QD. Dosing of study intervention will be organized by "cycles" of successive periods of 28 days. Participants will self-administer study intervention through the completion of Cycle 13. Participants will record compliance with study intervention dosing daily in their eDiary. At the end of each cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding cycle. Each subsequent cycle starts with the result of a home pregnancy test, which must be negative and entered in the eDiary for the participant to continue the study.

8.1.4.1. Site Visits

Participants will return to the clinic the first week after completion of Cycle 1 for Visit 3.

Subsequent site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur 1 week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Study medication will be dispensed at each visit. See the Schedule of Activities (see Table 1) for assessments required for each visit.

8.1.4.2. Telephone Visits

Approximately 6 weeks following each site visit, the participant will be contacted by telephone (Phone 3, Phone 4, Phone 5, and Phone 6). The first telephone contact will occur approximately 6 weeks after Visit 3. Telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with

daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

8.1.4.3. 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 participant'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 (hematology and chemistry), urine or serum pregnancy testing, study intervention compliance, and dispensation of study intervention may be conducted as needed. Consult with the medical monitor, if needed, to discuss unscheduled visit testing.

8.1.5. Post-Treatment Period

8.1.5.1. End-of-Treatment Visit

Two weeks after completion of Cycle 13, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on-treatment visits will be repeated, and final status assessed; in addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for liver tests and β-hCG to determine pregnancy. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

8.1.5.2. Early Termination Visit

If the participant does not complete the study for any reason (including investigator discretion), the reason and circumstances for the participant's early termination must be fully documented. If possible, the assessments specified for the follow-up/EOT visit (Visit 7) should be performed. The medical monitor should be consulted in advance of withdrawal whenever possible. Participants who are withdrawn from the study may not be re-enrolled.

8.1.5.3. Pregnancy Visit

If a participant becomes pregnant during the study, the site must discontinue the participant from study intervention immediately and have her return for a visit (see Table 1). In addition to the follow-up/EOT procedures the participant will undergo the following diagnostic procedures:

- Quantitative serum pregnancy test (unless pregnancy already confirmed by transvaginal ultrasound);
- Transvaginal ultrasonography to determine gestational age/estimated date of delivery (EDD).

8.1.6. Efficacy Evaluations

Planned time points for efficacy assessments are provided in the Schedule of Activities (see Table 1).

8.1.6.1. Pregnancy Testing

The contraceptive efficacy of relugolix combination therapy will be evaluated using the number of on-treatment pregnancies. On-treatment pregnancies are pregnancies with an estimated conception date (ECD) between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Pregnancy testing is conducted per the Schedule of Activities (see Table 1) as follows:

- A serum β-hCG pregnancy test is performed at Visit 1 and Visit 7. Serum testing is also performed during the study if a pregnancy is suspected or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound). A urine pregnancy test is performed at all site visits after screening and as needed;
- A home urine pregnancy test performed by the participant is required prior to the start of each cycle, and the result must be negative to continue on study. Any positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound when applicable).

8.1.6.2. Participant eDiary

All participants enrolled in the study will be provided a device with an application for a participant eDiary at Visit 2, along with detailed instructions for its use. Participants will complete daily eDiary entries including compliance with study intervention dosing, occurrence of sexual intercourse, use of back-up contraception, and home urine pregnancy test results. The eDiary data will be reviewed by the study staff on an ongoing basis and at specified timepoints as noted in the Schedule of Activities (see Table 1).

8.2. Safety Assessments

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), and clinical laboratory tests. Planned time points for all safety assessments are provided in the Schedule of Activities (see Table 1).

8.2.1. Physical Examinations

A complete physical examination, including gynecological and breast examination, will be conducted at Visit 1 and the follow-up/EOT visit (Visit 7). The examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. Height and weight will also be measured and recorded.

All other physical examinations should focus on signs and symptoms reported by the participant to assess for clinically significant changes from the baseline assessment.

The gynecologic examinations at screening will include testing for gonorrhea and chlamydia. Cervical cytology test must be conducted for participants 21 years or older (or who will become 21 years old during the trial) without an available test result from within 18 months years prior to the Screening Visit and submitted to the central laboratory. A repeat test should be performed for inadequate specimen and submitted to the central laboratory.

A bilateral breast examination will be performed at the time of the gynecologic examination.

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

8.2.2. Vital Signs

Vital signs including heart rate and systolic and diastolic blood pressure will be assessed. Vital signs will be measured with the participant in a seated position and should be preceded by at least 5 minutes of rest with the participant in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

Electrocardiograms are not routinely collected during the study and are to be performed per general clinical safety assessment, as applicable.

8.2.4. Clinical Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Table 1) for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within two weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Table 1).

If laboratory values from non–protocol -specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, serious adverse event, adverse event, or discontinuation of study intervention), then the results must be recorded in the eCRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

There will be ongoing monitoring of adverse events associated with mood disorders (see also Section 2.3.1).

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, considered related to the study

intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency of Collecting Adverse Event and Serious Adverse Event Information

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention. 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 intervention.

All serious adverse events will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event after conclusion of the study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse reports are provided in Appendix 3.

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 participant is the preferred method to inquire about adverse event occurrences.

The participant's eDiary entries 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 this instrument, proper follow-up with the participant 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.

8.3.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All serious adverse events and adverse events of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted. Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will review and then file it along with the [Investigator's Brochure] and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy Reporting

Details of all pregnancies will be collected after the start of study intervention and until the follow-up visit/EOT (Visit 7) (see Schedule of Activities, Table 1).

If a pregnancy is reported, study intervention should be withdrawn immediately and the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

8.3.6. Adverse Events of Clinical Interest

Adverse events of clinical interest in this study are defined as any increase in ALT or AST $\geq 3 \times$ 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 safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. Additional instructions for evaluating participants with an increase in ALT or AST $\geq 3 \times$ ULN may be found in Appendix 5.

8.3.6.1. Criteria for Temporary Withholding of Study Intervention 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 intervention should be immediately withheld with appropriate clinical follow-up (including repeat laboratory tests, until the participant's laboratory profile has returned to normal/baseline status), and the event reported per Section 8.3.6 and as a serious adverse event if serious adverse event criteria met, including the underlying diagnosis, as available:

- ALT or AST > 8 × ULN; or
- ALT or AST > 5 × ULN and persists for more than 2 weeks; or
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5; or
- ALT or AST > 3 × 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.

8.3.6.2. Criteria for Permanent Discontinuation of Study Intervention in Association with Liver Test Abnormalities

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

1. ALT or AST increases to ≥ 3 × ULN; AND
2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × 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 intervention treatment should be withheld or permanently discontinued as appropriate for the safety of the participant.

8.3.7. Adverse Events Related to Menstrual Bleeding

To ensure consistent reporting, the terms below should be used when participants report alterations from their usual menstrual bleeding pattern that meet adverse event reporting criteria. Select the term that most closely reflects both the volume of the menstrual flow and the frequency/duration/regularity of the bleeding episodes.

- Amenorrhea: Absence of menstrual bleeding

- Spotting Vaginal: Spotting regardless of the frequency/duration/regularity
- Oligomenorrhea: Infrequent bleeding/light or normal volume
- Polymenorrhea: Frequent bleeding/light or normal volume
- Menorrhagia: infrequent or regular frequency bleeding/ heavy volume OR prolonged bleeding regardless of flow volume
- Hypomenorrhea: regular frequency/light volume
- Metrorrhagia: irregular frequency/light or normal volume
- Menometrorrhagia: irregular bleeding/heavy volume

8.4. Treatment of Overdose

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

For this study, the protocol-specified dose of relugolix combination therapy is one tablet once daily. 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 participant for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a safety report form according to Appendix 3 whether or not the overdose is associated with an adverse event;
- Document the quantity of the excess dose as well as the duration of the overdosing in the Overdose eCRF page.

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Health Economics/ Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no hypothesis associated with the primary endpoint.

9.2. Sample Size Determination

9.2.1. Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 5,000 treatment cycles at-risk for pregnancy in participants 18 to 35 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of 13 28-day cycles;
- 45% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 4 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

9.2.2. Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% confidence interval (CI) for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$ where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100-woman years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with FDA Guidance for Industry (FDA 2019).

With at least 5000 on-treatment cycles at-risk for pregnancy (~ 400 woman-years), the study will have approximately 90% power for the upper bound of the 95% two-sided CI for the PI to be below 5.

Approximately 900 participants must be enrolled to achieve at least 5000 at-risk cycles. Taking into account a screening failure rate of 15%, a total of approximately 1060 participants will be screened.

The number of at-risk cycles will be monitored, and enrollment will be adjusted to ensure that at least 5000 on-treatment at-risk cycles are achieved the end of the study.

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.2.3. Sample Size Reassessment

To ensure that the trial is adequately powered for the evaluation of contraceptive efficacy measured by Pearl Index (PI), sample size reassessment will be performed periodically to check the key assumptions used for sample size calculations. In particular, the PI will be calculated from interim data to check the accuracy of the assumption (PI = 2) used for the initial sample size calculation. The planned sample size of 900 participants may be adjusted from the interim calculation to ensure the study is adequately powered to evaluate contraceptive efficacy. The detailed methodology for the sample size reassessment during the trial will be described in the statistical analysis plan.

9.3. Populations for Analyses

The analysis populations are defined in Table 6.

Table 6: Study MVT-601-050 Analysis Populations

Analysis Population	Description
Enrolled	All participants who sign the ICF
Intent-to-Treat (ITT)	All participants who receive at least one dose of study intervention
Modified Intent-to-Treat (mITT)	The subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred
Per-Protocol (PP)	The subset of participants in the rITT population with at least one treatment cycle that is also without specific protocol deviations
Restricted Intent-to-Treat (rITT)	The subset of participants included in the ITT population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred

Abbreviations: ICF = informed consent form.

9.4. Statistical Analyses

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be finalized prior to database lock. This section provides a summary of the planned statistical analyses of the endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

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 participants. Categorical data will be summarized by counts and percentages.

The single, final analysis of all efficacy and safety data will occur after approximately 900 participants have enrolled and been followed for thirteen cycles, if not early terminated.

9.4.2. Evaluable Cycles and Pearl Index Definitions

Evaluable cycles are defined below and will contribute to the denominator for calculating each type of PI.

- At-Risk PI (primary efficacy endpoint): Cycles without use of any other contraceptive methods and with confirmed vaginal intercourse (At-Risk Cycles).
- Gross PI: On-treatment cycles.
- Modified At-Risk PI: Cycles without use of any other contraceptive methods regardless of occurrence of vaginal intercourse.
- Method Failure PI: At-Risk Cycles without major protocol deviations.

9.4.3. Primary Endpoint

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment:

$$\text{Pearl Index (PI)} = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{number of 28-day at-risk cycles of treatment}}$$

There is no hypothesis associated with the primary endpoint. The primary contraceptive efficacy will be assessed by the point estimate of At-Risk PI and corresponding 95% CI. On-treatment pregnancies are pregnancies with an ECD between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the EDD will be ascertained. The ECD will be calculated as:

$$\text{EDD} - 38 \text{ weeks} = \text{ECD}$$

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses or β-hCG level.

The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse. The numerator and denominator in the At-Risk PI calculation are slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, as the primary contraceptive efficacy analysis, will be conducted using an rITT population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred . The At-Risk PI will be presented together with the two-sided 95% CI calculated based on a Poisson distribution (Benda et al. 2004).

9.4.4. Secondary Endpoints

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution. Specifically:

- The Gross PI will be estimated using the ITT population, defined as participants 18 to 35 years of age at the time of enrollment who have entered the study and have at least one on-treatment cycle.
- The modified PI will be estimated using the modified ITT (mITT) population, defined as the subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred .
- The Method Failure PI will be estimated using the per protocol analysis population, defined as the subset of participants in the rITT population, with at least one treatment cycle that is also without specific protocol deviations. For calculation of the

Method Failure PI, only pregnancies with a conception date during at-risk cycles that were also per protocol are included in the numerator.

- Cumulative 1-year pregnancy rate will be calculated on each of the analysis populations by the Kaplan-Meier (KM) survival analysis. All participants will be followed until they either have an outcome of pregnancy or are censored at the time of their last follow-up. The unit of time in the KM analysis will be the cycle, with pregnancies recorded by cycle of conception. Unlike the PI calculations, cycles based on use of adjunctive contraception will not be excluded.

9.4.5. Tertiary/Exploratory Endpoint(s)

Not applicable.

9.4.6. Safety Endpoints

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using MedDRA Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention treatment, and severity. An adverse event reported more than once for a participant is counted once at the maximum severity or strongest relationship to study intervention treatment when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

9.4.7. Other Analyses

Not applicable.

9.5. Interim Analyses

No formal interim analyses are planned for this study.

9.6. Data Monitoring Committee

This is an open-label single-arm study, and no Data Monitoring Committee will be convened. The safety of study participants will be closely monitored on an ongoing basis by Myovant Sciences representatives in close consultation with the Drug Safety and Pharmacovigilance Department. Issues identified will be addressed; this could involve, for example, amendments to the study protocol, and letters to investigators.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/(independent ethics committee) IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosures

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants undergoing rescreening will sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

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

Data Quality Assurance

Documentation Accountability

- All participant data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the completion of the informed consent process by the first participant and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. CLINICAL LABORATORY TESTS

- All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the protocol Schedule of Activities (see Table 1).
- Laboratory requisition forms must be completed, and samples must be clearly labeled with the Participant 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 7.
- Investigators must document their review of each laboratory safety report.
- Local laboratory results are only required in the event that central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7: Study MVT-601-050 Protocol-Required Safety Laboratory Assessments

Chemistry	**Hematology**	**Other**
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Liver tests: Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase LDH	WBC Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Serum Pregnancy Test (β-hCG) Urine Pregnancy Test Hemoglobin A1C International normalized ratio (INR)
	Lipid Profile	**Serology**
	Total Cholesterol Low Density Lipoprotein High-Density Lipoprotein Triglycerides	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody Hepatitis D antibody Hepatitis E antibody Epstein-Barr Virus

Abbreviations: β-hCG= beta human chorionic gonadotropin; LDH = lactic acid dehydrogenase; RBC = red blood cells; WBC = white blood cell.

APPENDIX 3. ADVERSE EVENTS DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an adverse event per definition above, then it cannot be a serious adverse event even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient 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 disability/incapacity

- 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 with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgement should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include 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.

Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and/or Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event or serious adverse event information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or their representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event or serious adverse event.

Assessment of Intensity

The investigator will make an assessment of intensity for each adverse event and serious adverse event reported during the study according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). For terms not specified with the CTCAE, the criteria below should be used to determine the grade severity:

Severity 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

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each adverse event.
A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
The investigator will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each adverse event, the investigator **must** document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to PHV-Myovant@quintiles.com. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event to PHV-Myovant@quintiles.com.

The investigator may change his/her opinion of causality in light of follow-up information and send a Safety Report Form follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions are to be used for the relationship of the adverse event to study intervention:

- **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.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to PHV-Myovant@quintiles.com within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to IQVIA RDS, Inc. via Paper CRF

- E-mail transmission of the Safety Report Form paper CRF is the preferred method to transmit this information to the global safety database.
- In rare circumstances and in the absence of e-mail or e-fax equipment, notification by telephone is acceptable with a copy of the Safety Report Form data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Safety Report Form within the designated reporting time frames.
- Contacts for serious adverse event reporting follow:

Using a Safety Report Form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study intervention.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Safety Report Form and is as follows:

Site Location	E-mail (Primary Reporting Method)	Fax Number (Secondary Reporting Method)
All Regions	[redacted]	[redacted]

For questions regarding serious adverse event or adverse event of clinical interest reporting, please call:

- North/South America: [redacted]
- Regional toll-free phone and fax lines distributed separately.

The initial report should include:

- Study number (MVT-601-050)
- Site address and number
- Investigator name
- Participant ID number, sex, and age
- Details of study intervention 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 intervention

If the participant 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 intervention 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, stabilization, the event is otherwise explained, or the participant is lost to follow-up. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

APPENDIX 4. COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the pregnancy report form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be a serious adverse event and will be reported as such.
- Any post-study pregnancy related serious adverse event considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention immediately and return for a Pregnancy visit as described in Section 8.1.5.3.

APPENDIX 5. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Study intervention (relugolix combination therapy) should be withheld for any liver test abnormality listed in Section 8.3.6, 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 Table 8, and per the investigations in Table 9. If close monitoring is not possible, study intervention should be withheld even if the results do not meet the criteria for withholding in Section 8.3.6.

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

Table 8: Study MVT-601-050 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (ALT, AST, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If ALT or AST ≥ 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 participant is asymptomatic	Frequency may decrease

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

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

Table 9: Study MVT-601-050 Investigations and 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 Table 8; • 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).

Abbreviations: CBC = complete blood count; INR = International normalized ratio.
Note: If the first follow-up test does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

APPENDIX 6. GUIDANCE FOR STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The novel coronavirus 2019 (COVID-19) pandemic has impacted the conduct of clinical trials globally. Regional quarantine laws, travel restrictions, and site closures present challenges to normal study conduct and may lead to missed study visits or procedures or an interruption to a patient's study drug supply.

Myovant Sciences has thoroughly reviewed guidance documents from various country and regional regulatory agencies and has put mitigation plans in place to ensure that the safety of patients is maintained, the study continues to be conducted in compliance with Good Clinical Practice (GCP), and risks to the integrity of the study are minimized. These plans will remain in place through the duration of the COVID-19 pandemic.

Safety During the COVID-19 Pandemic

Protecting study patients, investigational site staff and clinical service providers involved in Myovant Sciences clinical studies from activities that may unnecessarily increase the risk of contracting COVID-19 is of utmost importance. Regulations and policies instituted for safety purposes during the COVID-19 pandemic at the institutional, local, country, and regional level should be adhered to.

Protocol Adherence

Wherever possible and safe, study visits and procedures must be performed as outlined in the protocol to ensure patient safety and to maintain the integrity and interpretability of the study data. While modifications to normal study conduct may, in some cases, be necessary and unavoidable, they must be documented and reported where in conflict with the study protocol and this guidance. Deviations from the protocol will be documented, but those resulting specifically from the COVID-19 pandemic will be marked as such. All deviations resulting from the COVID-19 pandemic will be summarized in the clinical study report.

Visit Schedules and Study Procedures

Local policies, institutional restrictions, and/or patient ability/willingness to make site visits may curtail the ability to adhere to the in-person, on-site visit schedule required by the protocol. Investigators at clinical sites should evaluate the appropriateness of an on-site study visit during the COVID-19 pandemic.

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, as close to the visit target date as possible, taking all measures to prevent contracting COVID-19.

- All protocol-required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, Investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.

- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the Myovant medical monitor for consultation as necessary.

If the clinical study site is closed or the patient is unable/unwilling to attend on-site study visits due to the COVID-19 pandemic, alternative methods for completing assessments (eg, phone contact or virtual visit) should be implemented.

- Investigators must assess and evaluate the patient's continued participation and dosing with limited safety assessment.
- At a minimum, investigational site staff should make every attempt to contact the patient via telephone when an expected visit is due or missed to assess for adverse events, document concomitant medications, and study drug dosing since the last study visit.
- If the safety blood draws cannot be performed through the central laboratory per protocol, the investigator may advise the patient to have blood drawn at a local laboratory if there is a safety concern. If two consecutive study visits are missed and the patient is unable to return to the site, the investigator should advise the patient to have protocol-specified safety labs completed at a local laboratory to assess for any safety concerns. In both cases, the local laboratory results should be documented in the eCRF.
- Investigational sites should report all serious adverse events, adverse events of clinical interest, overdose, and pregnancy that the patient reports during these calls within 24 hours of awareness.
- Patients should be reminded of the importance of taking study drug daily or of using back-up contraception if study drug is interrupted.
- Study patients should continue to complete their daily eDiary, even if they run out of study drug, and site staff should motivate them to do so.

Patients should have the contact details of the investigational site medical staff to report any medical issues, including adverse events they may experience in real time.

As soon as the study patients are able to return to the investigational site for an on-site visit, they should do so. The next scheduled visit should occur on the target date as per the Schedule of Activities (see Table 1).

Study Participant Study Drug Supply

If a regional lockdown, travel restrictions, or site closure is imminent due to the COVID-19 pandemic, sites are encouraged to dispense additional study drug at an expected study visit or request patients to return for an unscheduled visit for additional study drug dispensation so patients have sufficient supply until their next upcoming visit. Patients should be instructed to

contact the site to report any medical issues they may experience and site staff should communicate with the patients to determine if it is appropriate for the patient to continue dosing with study drug if/when in-person study visits are not possible.

For cases where study patients are unable to visit the investigational site to pick up study drug, a direct-to-patient delivery of study drug by site staff or shipment via contracted courier may be possible. Consent authorizing direct-to-patient supply will be obtained. Sites should defer to national guidance on how this will occur. Where permitted by national guidance, verbal consent will be taken via telephone or video call and noted in the patient's source file. Where required, by national guidance, this will be followed up with written consent during the next clinic visit. Every effort will be made to obtain the patient's written consent for direct-to-patient delivery prior to delivery or shipment, where this is required by national guidance.

In the event that none of the above are possible for participants to continue taking study medication, a patient may need to be discontinued per the study protocol. Such decisions will be made on a case-by-case basis in discussion with the investigator and medical monitor.

On-Site Study Monitoring Restrictions

In the event study monitors/clinical research associates are not allowed to travel and/or return to a clinical site to monitor and source document verify study data, Myovant has developed plans to ensure monitors:

- Remotely verify source documentation as much data as reasonably possible without burdening sites, if allowed by the study site and country regulations, focusing on pages key to the interpretability of the study and the safety of participants.
- Remotely monitor study data through cross checking of various systems housing patient data against what is captured in the eCRFs.

Additional guidance on conducting clinical trials during the COVID-19 pandemic may be found in the following documents released by Regional Health Authorities, which may be updated (updates supersede the versions listed here):

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated June 03, 2020);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (28 April 2020).

APPENDIX 7. ABBREVIATIONS

List of Abbreviations and Definition of Terms

Abbreviation	Definition
β-hCG	beta human chorionic gonadotropin
AGC	atypical glandular cell
AGUS	atypical glandular cells of undetermined significance
AIS	adenocarcinoma in situ
ALT	alanine aminotransferase
ASC-H	atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
ATE	arterial thrombotic or thromboembolic event
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	novel coronavirus 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
E2	estradiol
ECD	estimated conception date
eCRF	electronic case report form
EDD	estimated date of delivery
eDiary	electronic diary
EOT	end-of-treatment
FDA	Food and Drug Administration
FDC	fixed-dose combination (tablet)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent-to-treat
LH	luteinizing hormone
LSIL	low-grade squamous intraepithelial lesion
NETA	norethindrone acetate
PI	Pearl Index
QD	once daily
QTcF	QTc corrected using Fridericia's formula
rITT	restricted intent-to-treat
STD	sexually transmitted disease
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

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Clinical Study Protocol

Protocol Title:	A Phase 3, Single-Arm, Open-Label Study to Evaluate the Contraceptive Efficacy of Relugolix Combination Therapy in Healthy Women 18 to 35 Years of Age Who are at Risk for Pregnancy
Protocol Number:	MVT-601-050
Amendment Number:	Original
Compound:	Relugolix Combination Therapy (relugolix, estradiol, norethindrone acetate)
Study Phase:	Phase 3
Short Title:	A Phase 3 Contraceptive Efficacy Study of Relugolix Combination Therapy in Healthy Women Who are at Risk for Pregnancy
Sponsor Name:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Agency Identifier Numbers:	IND 076642 IND 131161
Approval Date:	12 AUG 2020

CONFIDENTIALITY STATEMENT

The information contained in this document, particularly unpublished data, is the property of or under control of Myovant Sciences GmbH, and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Myovant Sciences GmbH, except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

A Phase 3, Single-Arm, Open-Label Study to Evaluate the Contraceptive Efficacy of Relugolix Combination Therapy in Healthy Women 18 to 35 Years of Age Who are at Risk for Pregnancy

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

DocuSigned by:

[redacted]

12-Aug-2020 | 4:26 PM PDT

Date

12-Aug-2020 | 12:54 PM PDT

Date

12-Aug-2020 | 9:33 AM PDT

Date

12-Aug-2020 | 9:44 AM PDT

Date

INVESTIGATOR STATMENT

- 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)	Principal Investigator Signature
Clinical Site	Date

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Single-Arm, Open-Label Study to Evaluate the Contraceptive Efficacy of Relugolix Combination Therapy in Healthy Women 18 to 35 Years of Age Who Are at Risk for Pregnancy

Short Title: A Phase 3 Contraceptive Efficacy Study of Relugolix Combination Therapy in Healthy Women Who Are at Risk for Pregnancy

Protocol Number: MVT-601-050

Location: United States (US)

Study Centers: Approximately 40 sites

Study Phase: Phase 3

Target Population: Women 18 to 35 years of age who are at risk for pregnancy

Rationale:

This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy. Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis. Both conditions are prevalent in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy of relugolix combination therapy in treatment of symptoms associated with endometriosis or uterine fibroids, or the safety of patients undergoing treatment with relugolix combination therapy. By quantifying the contraceptive effectiveness of relugolix combination therapy (using the Pearl Index [PI]), results from this study will provide evidence for patients and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception while being treated with relugolix combination therapy.

Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

Overall Design:

Study MVT-601-050 is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy (relugolix 40 mg, estradiol [E2] 1 mg, and norethindrone acetate [NETA] 0.5 mg). Approximately 900 sexually active, healthy women 18 to 35 years of age who will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy.

The study consists of a Screening Period (Visit 1), a 52-week Treatment Period (Visits 2 to 6), and a 14-day Follow-Up Period (Visit 7).

Participant eligibility will be determined based on assessments performed at Visit 1, when the participant's medical and gynecological history (including contraception and use of prior medications) will be reviewed; their height, weight, and vital signs will be measured; and physical, gynecological, and breast examinations will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy, and participants will be screened for the sexually transmitted diseases (STDs) gonorrhea and chlamydia. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening.

Participants who meet all eligibility criteria will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Prior to initiation of treatment with relugolix combination therapy on Day 1 (Visit 2), continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. Participants must have a negative urine pregnancy test. Participants will also receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Finally, study medication will be dispensed, together with instructions for administration and back-up contraception, if applicable. The window for initiating dosing with relugolix combination therapy also depends upon contraceptive status. If Visit 2 occurs within the correct window, dosing may begin at Visit 2. Otherwise, the participant will initiate dosing at home when the appropriate window is reached and after another negative urine pregnancy test result is recorded in the eDiary. Thereafter, continuous treatment with relugolix combination therapy will be taken for 13 consecutive 28-day treatment cycles.

Throughout the Treatment Period, compliance with study intervention administration will be recorded daily in the eDiary. At the completion of each 28-day treatment cycle, the participant will record the results of a urine pregnancy test and indicate whether intercourse or use of additional contraception occurred during the previous 28-day treatment cycle. Each treatment cycle starts with the result of a home pregnancy test, the result of which must be negative and must be entered in the eDiary for a participant to continue in the study. Assessments of safety (physical, gynecological, and breast examinations; laboratory assessments; vital signs; etc.) will be performed throughout the study. Telephone visits to assess compliance and safety will be performed approximately 6 weeks following each on-site visit during the treatment period.

Fourteen days after discontinuation of treatment, a follow-up/EOT visit (Visit 7) will be conducted. All assessments done at on-treatment visits will be repeated and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for selected serum chemistry assessments, including β-hCG to determine pregnancy and safety assessments will be performed. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

Any participant who becomes pregnant during the study or is pregnant at the follow-up visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

Inclusion and Exclusion Criteria:

Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 35 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
6. Is willing to use the investigational product as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through the end of study participation;
7. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
8. Has body mass index (BMI) ≥ 18 kg/m^2;
9. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of VTE due to prolonged immobilization (eg, due to trauma, surgery, or other illness markedly limiting mobility) within 2 weeks prior to screening; plans for

surgery requiring prolonged immobilization during the study; has a hereditary or acquired predisposition to or elevated risk for venous or arterial thrombosis, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant); or has thrombogenic cardiac valve or rhythm abnormalities of the heart associated with thromboembolism (eg, atrial fibrillation);

Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.

3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end-organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

Note: The specific reasons for exclusion should be documented in the eCRF.

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (AST, ALT, total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

11. Has any of the following laboratory values:

a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
c. Fasting triglycerides > 150 mg/dL;
d. High-density lipoprotein level < 50 mg/dL.

12. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

13. Has a known history of infertility or sub-fertility;
14. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
15. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening, (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.

16. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, bleeding from cervical polyp, recurrent bleeding after intercourse).

Other Conditions/Disorders

17. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
18. Has known HIV infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
19. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
20. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants 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 or mental health professional's judgement, 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;

21. Has any disease that may worsen under hormonal treatment, such as known gall bladder disease or a hepatic hemangioma;
22. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the investigational product or its excipients;
23. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
24. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

25. Has a known or suspected pregnancy;
26. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
27. Is breastfeeding;

    Note: If recently stopped breastfeeding, must have resumed menstruation and must have had at least two normal menstrual cycles.

Concomitant and Recent Medications/Devices

28. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
29. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
30. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein).

Miscellaneous

31. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

Disclosure Statement: This is a single-arm, open-label study to evaluate the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy.

Number of Participants:

Approximately 1060 participants will be screened to achieve approximately 900 participants enrolled to study intervention. The sample size has been set to attain at least 5,000 treatment

cycles at-risk for pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse) in participants 18 to 35 years of age at the time of enrollment (see Section 9.2). Sample size reassessment will be performed periodically to check the key assumptions used for sample size calculations. If the interim data shows that the observed PI is likely greater than the expected PI (ie, PI = 2), the planned sample size of 900 participants will be reassessed and increased.

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study but do not participate in the study are not considered enrolled.

Intervention Groups and Duration:

Relugolix combination therapy (relugolix 40 mg, E2 1 mg, and NETA 0.5 mg) as a fixed-dose combination tablet is to be taken orally QD at approximately the same time each day, 1 hour before or 2 hours after a meal. Relugolix combination therapy is continuous; that is, a tablet is to be taken daily for the entire duration of the treatment period, without a drug-free interval.

Study intervention will be self-administered during 13 consecutive 28-day treatment periods ("Cycles"), for a total duration of 52 weeks.

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

Participants may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove participants from therapy under this protocol for reasons of safety and/or lack of compliance, as discussed below. Participants removed from study intervention for any reason will, if possible, undergo assessments for an early discontinuation visit (see Schedule of Activities, Section 1.3) approximately 14 days after the end of treatment (ie, after the participant's last dose of study intervention).

Criteria for Evaluation:

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the estimated date of delivery (EDD) will be ascertained. The estimated conception date (ECD) will be calculated as:

- EDD − 38 weeks = ECD

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses, or β-hCG level.

Statistical Methods:

<u>Contraceptive Efficacy</u>

This study has one primary endpoint, the At-Risk PI, calculated on the basis of the number of on-treatment pregnancies in the numerator and the number of at-risk cycles of exposure in the denominator. The numerator and denominator are thus slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, the primary contraceptive efficacy analysis, will be conducted using an restricted intent-to-treat (rITT) population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred (ie, a treatment cycle containing an ECD for a pregnancy). The At-Risk PI will be presented together with the two-sided 95% confidence interval (CI) calculated based on a Poisson distribution (Benda et al. 2004). There is no hypothesis associated with the primary endpoint.

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution.

Safety

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention, and severity. An adverse event reported more than once for a participant will be counted once at the maximum severity or strongest relationship to study intervention when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

Sample Size Determination

Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 5,000 treatment cycles at-risk for pregnancy in participants 18 to 35 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of thirteen 28-day treatment cycles;
- 45% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 4 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% CI for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$, where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100 woman-years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with the FDA Guidance for Industry (FDA 2019).

With at least 5000 on-treatment cycles at-risk for pregnancy (~ 400 woman-years), the study will have approximately 90% power for the upper bound of the 95% two-sided CI for the PI to be below 5.

Approximately 900 participants must be enrolled to achieve at least 5000 at-risk cycles. With the assumption of a screening failure rate of 15%, a total of approximately 1060 participants will be screened.

The number of at-risk cycles will be monitored, and enrollment will be adjusted to ensure that at least 5000 on-treatment at-risk cycles are achieved at the end of the study.

Sample Size Reassessment

To ensure that the trial is adequately powered for the evaluation of contraceptive efficacy measured by PI, sample size reassessment will be performed periodically to check the key assumptions used for sample size calculations. In particular, the PI will be calculated from interim data to check the accuracy of the assumption (PI = 2) used for the initial sample size calculation. The planned sample size of 900 participants may be adjusted from the interim calculation to ensure the study is adequately powered to evaluate contraceptive efficacy. The detailed methodology for the sample size reassessment during the trial will be described in the statistical analysis plan.

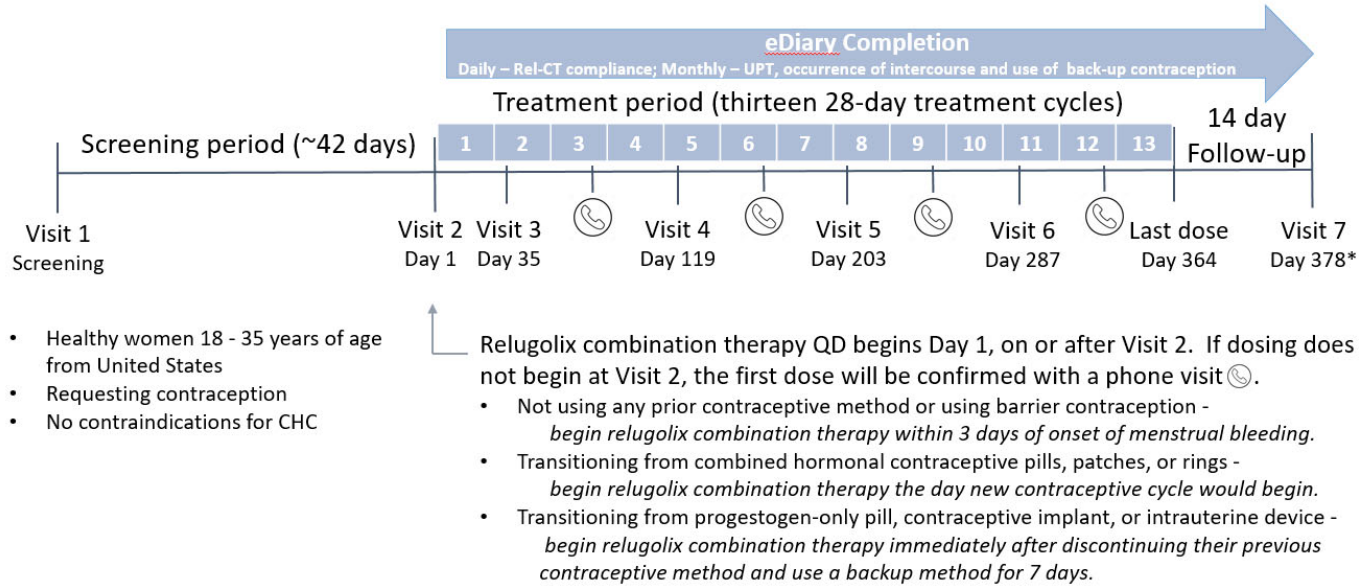
Data Monitoring Committee:

This is an open-label single-arm study, and no Data Monitoring Committee will be convened. The safety of study participants will be closely monitored on an ongoing basis by Myovant Sciences representatives in close consultation with the Drug Safety and Pharmacovigilance Department. Issues identified will be addressed; this could involve, for instance, amendments to the study protocol and letters to investigators.

1.2. Study Schema

The study schema is presented in Figure 1.

Figure 1: MVT-601-050 Study Schematic



Abbreviations: CHC = combined hormonal contraceptive; E2 = estradiol; eDiary = electronic diary; NETA = norethindrone acetate; QD = once daily; Rel-CT = relugolix combination therapy (relugolix 40 mg, E2 1 mg, NETA 0.5 mg); UPT = urine pregnancy test.
* or 14 days after the last dose.
Note: During the treatment period Visits occur approximately 7 days after the end of the previous cycle. Phone visits occurr approximately 6 weeks after the subsequent Visit.

1.3. Schedule of Activities

Table 1: Schedule of Activities for MVT-601-050

Trial Period	**Screening**	**Allocation**	**Treatment Period**							
Visit	**V1**	**V2[a]**	**V3**	**P3**	**V4**	**P4**	**V5**	**P5**	**V6**	**P6**
Visit Timing	**−42 D**	**On or prior to D1[b]**	**7 days after Cycle 1**	**~6 wks after V3**	**~7 days after Cycle 4**	**~6 wks after V4**	**7 days after Cycle 7**	**~6 wks after V5**	**7 days after Cycle 10**	**~6 wks after V6**
Day of Study Intervention Treatment[c]		**D 1[d]**	**D 35**	**D 77**	**D 119**	**D 161**	**D 203**	**D 245**	**D 287**	**D 329**
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X								
Medical History	X									
Gynecological History	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X
Contraceptive History	X	X								
Dispense eDiary		X								
eDiary Training/Re-Training[e]		X	X	X	X	X	X	X	X	X
Dispense Study Intervention		X	X		X		X		X	
eDiary Compliance/Data Review			X	X	X	X	X	X	X	X
Drug Accountability[f]			X		X		X		X	
Contraceptive Counseling									X[g]	X[g]
Physical Examination[h,i]	X									
GYN & Breast Examination[i]	X									
Height	X									
Weight, Vital Signs (HR, BP)	X	X	X		X		X		X	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory[j]	X						X			
Gonorrhea/Chlamydia Test	X									
Cervical Cytology[k]	X									
Serum β-hCG[l]	X									
Urine Pregnancy Test[m]		X	X		X		X		X	
Transvaginal ultrasound										

Table 1: Schedule of Activities for MVT-601-050 (Continued)

Trial Period	**Post-Treatment Period**		
Visit	**Follow-Up/EOT (V7)[n]**	**Pregnancy**	**Unscheduled**
Visit Timing	**14 days after Cycle 13 or Last Dose**	**Upon diagnosis**	
Day of Study Intervention Treatment[c]	**D378**	**NA**	**NA**
Informed Consent			
Inclusion/Exclusion Criteria			
Medical History			
Gynecological History			
Prior and Concomitant Medication Review	X	X	X
Contraceptive History			
Dispense eDiary			
eDiary Training/Re-Training[e]			X[p]
Dispense Study Intervention			X[p]
eDiary Compliance/Data Review	X	X	X[p]
Drug Accountability[f]	X	X	X[p,q]
Contraceptive Counseling	X[g]		
Physical Examination[h,i]	X	X	X[p]
GYN & Breast Examination[i]	X	X	X[p]
Height			X[p]
Weight, Vital Signs (HR, BP)	X	X	X[p]
Adverse Event Monitoring	X	X	X
Clinical Laboratory[j]	X	X	X[p]
Gonorrhea/Chlamydia Test			X[p]
Cervical Cytology[k]			X[p]
Serum β-hCG[l]	X	X	X[p]
Urine Pregnancy Test[m]	X		X[p]
Transvaginal ultrasound		X[o]	

Abbreviations: β-hCG = beta human chorionic gonadotropin; AGC = atypical glandular cells; AGUS = atypical glandular cells of undetermined significance; AIS = adenocarcinoma in situ; ALT = alanine transaminase; ASC-H = atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion; ASCUS = atypical squamous cells of undetermined significance; AST = aspartate transaminase; BP = blood pressure; D = day(s); EDD = estimated date of delivery; eDiary = electronic diary; EOT = end-of-treatment; GGT = gamma-glutamyltransferase; GYN gynecologic; HPV = human papilloma virus; HR = heart rate; HSIL = high-grade squamous intraepithelial lesion; LDH = lactic dehydrogenase; LSIL = low-grade squamous intraepithelial lesion; NA= not applicable; P = phone contact; V = visit.

a. The timing of Visit 2 depends on contraceptive status at screening and the need for washout. Visit 2 should occur after screening tests results indicating eligibility are available.

b. Study intervention dosing (Day 1) occurs during the allocation period (Visit 2). The timing of Day 1 may vary based on the following:

- For participants not using any prior contraceptive method or using barrier contraception Day 1 must occur within 3 days of the onset of menses and after a negative urine pregnancy test has been recorded in the participant's eDiary. If Visit 2 occurs within 3 days of the onset of menses, the participant will begin her first treatment cycle of relugolix combination therapy dosing at the study visit. If the visit is not within this window, dosing will begin once the participant reports the onset of the next menses, followed by entry of a negative urine pregnancy test result in the eDiary. The eDiary will then instruct the participant to take and record the first dose of study intervention.
- For participants transitioning from combined hormonal contraceptive pills, patches, or rings: Day 1 is the day she would normally initiate a new contraceptive cycle. If Visit 2 cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new contraceptive cycle, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.
- For participants transitioning from progestin-only pills: Visit 2/Day 1 must be scheduled the day after completing treatment with the prior method and the participant must use a back-up method for the first 7 days of relugolix combination therapy.
- For participants using a contraceptive implant or intrauterine device: Visit 2/Day 1 must be scheduled the day the implant or device is removed. The participant must use a back-up contraceptive method for the first 7 days of relugolix combination therapy.

c. Visits should be scheduled on the target day of study intervention treatment as indicated. If this this not feasible, the visit should occur as soon after the target day as possible. Treatment must not be extended beyond Day 364.
d. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact.
e. Initial eDiary training to be performed when eDiary is dispensed. eDiary training for the participant should be performed/reinforced throughout the study.
f. The participant should be asked to bring all study intervention to the clinic for each visit (see Section 6.4).
g. Counseling regarding post-trial contraceptive use should be provided to all participants at Visit 6 and repeated at Phone Visit 6 and Visit 7 (Follow-up/EOT).
h. A complete physical exam will be conducted at Visit 1 and Visit 7 and will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All other physical examinations should focus on signs and symptoms reported by the participant.
i. Physical, gynecologic, and breast examinations should be conducted by a licensed health professional (eg, physician, nurse practitioner, physician assistant).
j. Clinical laboratory tests will include hematology, chemistry, lipid profile, and Hemoglobin A1C at screening. The screening sample must be obtained in the fasted state (no food or drink other than water after midnight). If the screening period is extended by more than 6 weeks for any reason, screening laboratories (chemistry and hematology) should be repeated prior to administration of the first dose of study intervention. Assessments at Visits 5 and 7 will be limited to liver tests (ALT/AST/GGT/total bilirubin/alkaline phosphatase/LDH).
k. Cervical smear is only applicable to participants 21 years of age and older (or who will become age 21 during the course of the trial). Cervical cytology does not need to be performed if a normal cervical smear (ie, no evidence of ASCUS with high-risk HPV positive, ASC-H, LSIL, HSIL, squamous cell carcinoma, AGUS, AGC-neoplastic or AIS) performed within 18 months of Visit 1 can be documented and the participant does not report a history of abnormal results within the past 3 years. Cervical smear may be performed by a nurse practitioner or physician's assistant if licensed in the state, is trained, and it is within their scope of practice.
l. A serum β-hCG pregnancy test is required at Visit 1 and Visit 7 (Follow-up/EOT). Serum testing should also be performed during the trial if a pregnancy is suspected, or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound).

m. A urine pregnancy test will be performed at each site visit after screening. Additionally, a home urine pregnancy test performed by the participant is required prior to the start of each cycle and the result must be negative to continue. Any positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound, when applicable).
n. Follow-up/EOT visit also to be done in case of early discontinuation.
o. Transvaginal ultrasonography will be performed to determine gestational age/EDD.
p. For an unscheduled visit, these procedures will be performed as needed, based on the reason(s) for the Unscheduled visit.
q. eDiary and any remaining drug should be collected by the site at this visit.

2. INTRODUCTION

Relugolix is a daily, orally active, potent, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist being developed in combination with estradiol (E2) and norethindrone acetate (NETA) (relugolix combination therapy) for the treatment of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Relugolix competitively binds to GnRH receptors on gonadotrophic neurons, blocking endogenous GnRH from binding to and subsequent activation of GnRH receptors, preventing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are considerably reduced, with the reduction in FSH concentrations preventing natural follicular growth and development, limiting the production of estrogen by the developing ovarian follicles and secretion into the systemic circulation. Further, prevention of an LH surge inhibits ovulation, and therefore the corpus luteum does not develop, which precludes the production and secretion of progesterone into the systemic circulation. Relugolix is combined with E2 1 mg and NETA 0.5 mg to maintain E2 concentrations within a therapeutic range and progesterone/progestin concentrations at low levels, to treat symptoms associated with endometriosis and uterine fibroids while maintaining BMD and preventing vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen.

Relugolix combination therapy is intended to provide an effective and well-tolerated option for the long-term treatment of symptoms associated with endometriosis and uterine fibroids. This study will evaluate the efficacy and safety of relugolix combination therapy as a contraceptive.

2.1. Study Rationale

Myovant is developing relugolix combination therapy for the indications of heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

Uterine fibroids and endometriosis are both prevalent conditions in women of reproductive age; thus, it is expected that many women being treated with relugolix combination therapy may also seek an effective contraceptive method. Given the mechanism of action of relugolix combination therapy, concomitant use of hormonal contraceptives could negatively affect the efficacy or safety of participants undergoing treatment with relugolix combination therapy for the treatment of symptoms associated with endometriosis or uterine fibroids. This study is intended to demonstrate the contraceptive efficacy of relugolix combination therapy.

This study is being conducted in women of reproductive age with presumed normal fertility rather than in women with symptomatic uterine fibroids or endometriosis because those conditions may be associated with subfertility, which would confound assessment of the intrinsic contraceptive effectiveness of relugolix combination therapy. By determination of the Pearl Index (PI) for relugolix combination therapy (ie, by quantifying the contraceptive effectiveness), the study will provide evidence for participants and their healthcare providers to make an informed decision about the need to use additional non-hormonal contraception during treatment with relugolix combination therapy.

2.2. Background

Replicate, randomized, double-blind, placebo-controlled, 24-week phase 3 studies followed by a long-term open-label extension study were conducted within each indication to support marketing approval.

To support the uterine fibroid indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with heavy menstrual bleeding associated with uterine fibroids. Patients with confirmed uterine fibroids with heavy menstrual bleeding were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (Studies MVT-601-3001 [N = 387] and MVT-601-3002 [N = 381]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3003), designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the uterine fibroid indication.

A statistically greater proportion of women treated with relugolix combination therapy compared to placebo (73.4% vs. 18.9% [$p < 0.0001$] in MVT-601-3001 and 71.2% vs. 14.7%% [$p < 0.0001$] in MVT-601-3002) achieved the primary endpoint of both a menstrual blood loss volume of < 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment. Six key secondary endpoints related to menstrual blood loss volume, amenorrhea, change in hemoglobin, pain associated with uterine fibroids as measured by a Numerical Rating Scale, and change in patient-reported distress from heavy bleeding, passing of blood clots, and pelvic pressure as assessed by the validated Bleeding and Pelvic Discomfort scale, and change in uterine volume were also met. Relugolix combination therapy maintained BMD at levels comparable to placebo over 24 weeks and was generally well tolerated. Additionally, the long-term extension study MVT-601-3003 demonstrated durability of treatment effect for up to 52 weeks. The overall safety profile of relugolix combination therapy for up to 52 weeks was consistent with that observed over the first 24 weeks with low incidence of vasomotor symptoms and maintenance of BMD over time.

To support the endometriosis indication, the safety and efficacy of relugolix combination therapy was assessed in two replicate, phase 3, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 1250 premenopausal women with pain associated with endometriosis. Patients with confirmed endometriosis with moderate to severe pain were randomized to receive either relugolix combination therapy for 24 weeks, relugolix monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks, or placebo for 24 weeks (MVT-601-3101 [N = 628] and MVT-601-3102 [N = 622]). Patients who completed their 24-week study and met other eligibility criteria were eligible to enter the open-label extension study (MVT-601-3103) designed to evaluate the long-term safety and efficacy of relugolix combination therapy in the endometriosis indication.

Patients receiving relugolix combination therapy achieved both co-primary endpoints by demonstrating clinically-meaningful pain reductions compared to placebo for dysmenorrhea (74.5% vs. 26.9% [$p < 0.0001$] in MVT-601-3101 and 75.2% vs. 30.4% [$p < 0.0001$] in MVT-601-3102) and for nonmenstrual pelvic pain (58.5% vs. 39.6% [$p < 0.0001$] in MVT-601-3101 and 66% vs. 42.6% [$p < 0.0001$] in MVT-601-3102).

In study MVT-601-3101, all seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, and impact of pain on daily activities as measured by the Endometriosis Health Profile-30 (EHP-30) pain domain, greater proportions of women not using analgesics (p-values < 0.0001), changes in mean nonmenstrual pelvic pain (p = 0.0002), greater proportions of women not using opioids (p = 0.0005), and changes in mean dyspareunia (painful intercourse; p = 0.0149). In study MVT-601-3102, six of seven key secondary endpoints measured at Week 24 achieved statistical significance compared with placebo, including changes in mean dysmenorrhea and overall pelvic pain, impact of pain on daily activities as measured by the EHP-30 pain domain, a greater proportion of women not using opioids (all p-values < 0.0001), changes in nonmenstrual pelvic pain (p = 0.0012), and dyspareunia (painful intercourse; p = 0.0371). Relugolix combination therapy was generally well tolerated with minimal BMD loss over 24 weeks.

In addition, an ovulation inhibition study with relugolix combination therapy in healthy adult premenopausal women has been completed (MVT-601-046, N = 67). This open-label, single-arm study included a pre-treatment period to confirm ovulatory status, an 84-day treatment period to assess the effects of relugolix combination therapy on ovarian activity, and a post-treatment follow-up period to determine time to return of ovulation. Ovulation (as assessed by the Hoogland-Skouby scale [Hoogland and Skouby 1993]) was inhibited for 100% of participants during the entire 84-day treatment period, and ovarian activity, as evidenced by the degree of follicular growth, was markedly suppressed. Pituitary secretion of FSH and LH, and ovarian production of estradiol and progesterone were markedly suppressed with relugolix combination therapy, with median E2 serum concentrations consistently maintained within an approximate range of 30 to 40 pg/mL during the 84-day treatment period. Mean progesterone concentrations were consistently maintained between 0.94 and 1.25 nmol/L, with individual values all below 5 nmol/L, the cut-off value for luteal activity in the Hoogland-Skouby assessment scale, consistent with the suppression of ovulation observed across all three treatment periods. Additionally, endometrial proliferation was suppressed with relugolix combination therapy, with endometrial thickness consistently maintained between 4 and 5 mm and likely contributing to the reduction in overall bleeding. All women returned to ovulation or began menses upon discontinuation of relugolix combination therapy demonstrating the revisability of the treatment effect. The mean time to ovulation following discontinuation of relugolix combination therapy was 23.5 days, with 97.01% (65 of 67 participants) having a confirmed ovulation within 36 days post treatment (one participant ovulated on Day 43 and the other began menstruation on Day 39).

As of January 2020, the relugolix clinical development program includes data from 3258 participants and patients exposed to relugolix either as monotherapy or as relugolix combination therapy. These data include single doses up to 360 mg and multiple doses up to 120 mg administered for more than a year. Data from the pivotal phase 3 studies in the uterine fibroid indication demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. Data from the pivotal phase 3 studies in the endometriosis indication also demonstrate robust efficacy with a safety and tolerability profile similar to that of placebo. These collective data continue to support a favorable benefit/risk profile for the proposed indications. By the time this contraception study is completed, it is expected that over 1500 participants and patients will have received relugolix combination therapy, with over

500 participants and patients having received relugolix combination therapy for 1 year and over 200 participants and patients for up to 2 years.

In summary, data from the relugolix nonclinical, pharmacodynamic, and clinical development program support the proposed mechanism of action for relugolix combination therapy, which works through inhibition of follicular development and prevention of ovulation, suppressing the secretion of endogenous estradiol and progesterone. Data from the completed pivotal phase 3 studies demonstrate robust efficacy results for the indications studied. Data from the ovulation inhibition study demonstrate maximal suppression of ovulation. The currently available safety database is large and allows characterization of the safety profiles of relugolix monotherapy and relugolix combination therapy to support initiation of this study. A detailed description of the chemistry, pharmacology, efficacy, and safety of relugolix is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of relugolix combination therapy may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

On the basis of nonclinical studies, clinical safety analyses, and data available for investigations of similar compounds, relugolix combination therapy may be associated with potential risks. The risk assessment and mitigation strategies for this protocol are outlined in

Table 2.

Table 2: Study MVT-601-050: Risk Assessment and Mitigation Strategies

Potential Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Hepatic Transaminase Elevation Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver biochemical tests are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 × ULN; total bilirubin values > 1.5 × ULN.	Hepatic transaminases are monitored closely in accordance with FDA drug-induced liver injury guidelines (FDA 2009) in all relugolix studies. Abnormal liver tests (AST or ALT > 3 × ULN) that develop during the randomized treatment period will be reported within 24 hours of study personnel awareness.
Embolic and Thrombotic Events Oral contraceptives and hormone replacement therapy are associated with an increased risk for a venous or arterial thromboembolic event.	Exclusion of participants with previous or current venous thromboembolism.	Active monitoring of adverse events.
Embryofetal Toxicity In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures similar to those at the recommended human dose. No effects on embryofetal development were observed in rats in a similar study. In both rabbits and rats, no fetal malformations were present at any dose level tested that were associated with relugolix exposures similar to and approximately 733-times the exposures in women at the recommended human dose, respectively. Based on these findings, exposure to relugolix combination therapy early in the first trimester of pregnancy has the potential to increase the risk of early pregnancy loss.	Exclusion of pregnant and lactating women.	Monthly pregnancy testing; immediate withdrawal for pregnancy.

Potential Risk	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Tumors (Breast and Liver) Breast cancer is a hormonally sensitive tumor. There is substantial evidence that combined oral contraceptives do not increase the incidence of breast cancer. Although past studies have suggested that combined oral contraceptives might increase the incidence of breast cancer, more recent studies have not confirmed such findings. Hepatic adenomas are associated with hormonal contraceptive use and a long-term increased risk of developing hepatocellular carcinoma.	Exclusion criteria for participants with known, suspected, or a history of breast cancer or active liver disease.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase. Active monitoring of adverse events.
Mood Disorders Depression has been reported with the prescribed use of GnRH receptor antagonists and agonists and with combined oral contraceptives and hormone replacement therapy.	Exclusion of participants whose mood disorder has been unstable or not well controlled. Exclusion of participants who have major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia, or other psychotic disorders based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria.	Active monitoring of adverse events.
Gallbladder Disease Combined hormonal therapy use may be associated with gallbladder disease.	Exclusion criteria for ALT and AST > 2 × ULN; total bilirubin values > 1.5 × ULN.	Active monitoring with routine clinical laboratory tests including ALT, AST, bilirubin, and alkaline phosphatase and adverse events is performed during the study.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; FDA = Food and Drug Administration; GnRH = gonadotropin-releasing hormone; ULN = upper limit of normal.

Adverse drug reactions associated with relugolix combination therapy in women with uterine fibroids include the nonserious adverse events of hot flush, abdominal pain, uterine bleeding, alopecia, libido decreased, irritability, hyperhidrosis, dyspepsia, and breast cyst and serious adverse events of uterine myoma prolapse and expulsion. Refer to the Investigator's Brochure for information on adverse events observed in the endometriosis program for relugolix combination therapy.

In completed phase 1, 2, and 3 studies, there were no drug-specific trends observed in mean or individual patient vital sign measurements, laboratory test results, or electrocardiogram parameters, with the exception of infrequent transient and predominantly mild hepatic transaminase elevations that were observed at a frequency comparable to that in placebo.

No new safety concerns have been identified during active ongoing monitoring.

Overall, the benefit/risk profile remains favorable for the continued development of relugolix combination therapy.

2.3.2. Benefit Assessment

Relugolix combination therapy is a once daily oral medication that has been shown to achieve 100% suppression of ovulation in an ovulation inhibition study (MVT-601-046), suggesting that with appropriate use it has the potential to be a highly effective contraceptive method. Additionally, prompt resumption of ovulation following discontinuation of relugolix combination therapy was observed, indicating the return to fertility is rapid and predictable.

The contraceptive action of relugolix combination therapy is mediated by relugolix, which suppresses follicular development and endogenous production of estrogen and progesterone. The risks of bone loss and vasomotor symptoms associated with a hypoestrogenic state, as well as endometrial hyperplasia from unopposed estrogen, are mitigated by administering relugolix in combination with E2 and NETA at low doses commonly used for hormone replacement therapy in menopause rather than the higher doses used in combined hormonal contraceptives to suppress ovulation. The low dosing of E2 and NETA in relugolix combination therapy may be considered an advantage to those who prefer to minimize the use of exogenous hormones.

Similar to continuous or extended cycle oral contraceptive regimens, relugolix combination therapy may benefit women who wish to limit cyclic bleeding for personal reasons. In the uterine fibroid studies, relugolix combination therapy was associated with an 84.3% reduction in menstrual blood loss volume and a high proportion of patients achieved amenorrhea (52.3% in MVT-601-3001 and 50.4% in MVT-601-3002). This change in the menstrual bleeding pattern may be considered as an advantage to some women.

Relugolix combination therapy has been generally well tolerated in most patients and participants, with an overall low rate of discontinuation due to adverse events.

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with relugolix combination therapy are justified by the anticipated benefits that may be afforded to participants in this study who seek effective contraception.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 3.

Table 3: Study MVT-601-050 Study Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
To assess the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy, as expressed by the At-Risk PI in the rITT population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse.	The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment: • PI = $\frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{Number of 28-day at-risk cycles of treatment}}$ On-treatment pregnancies are pregnancies with an estimated conception date between the first day of study intervention intake up to and including 7 days after the last intake of study medication. The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy, ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse.
Secondary Efficacy	
To assess the following for relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy:	
• Contraceptive efficacy, as expressed by the modified At-Risk PI, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy, regardless of occurrence of vaginal intercourse.	• Modified At-Risk PI: PI based on the number of on-treatment pregnancies occurring during cycles without any other contraceptive methods regardless of occurrence of vaginal intercourse.
• "Typical use" contraceptive efficacy, as expressed by the Gross PI, based on the number of on-treatment pregnancies occurring during all cycles in the ITT population, regardless of use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.	• Gross PI: PI based on the number of on-treatment pregnancies occurring during all cycles regardless of the use of other contraceptive methods, confirmed vaginal intercourse, or protocol compliance.
• "Perfect use" contraceptive efficacy, as expressed by the Method Failure PI, based on the number of on-treatment pregnancies in the PP population.	• Method Failure PI: PI based on the number of on-treatment pregnancies occurring during cycles that are at risk and without major protocol deviations.
• Contraceptive efficacy in various populations and analysis sets.	• Cumulative 1-year pregnancy rates.

Objectives	Endpoints
Safety	
• To describe the safety of relugolix combination therapy.	• Incidence of treatment-emergent adverse events, change in vital signs (including body weight), and clinical laboratory tests.
• To estimate discontinuation rate.	• Proportion of enrolled participants who do not complete 13 treatment cycles.

Abbreviations: ITT = intent-to-treat (Analysis Set); PI = Pearl Index; PP = per protocol (Analysis Set); rITT = restricted intent-to-treat (Analysis Set).

4. STUDY DESIGN

4.1. Overall Design

This is a single-arm, open-label, phase 3 study to assess the contraceptive efficacy of relugolix combination therapy. Approximately 900 sexually active, healthy women 18 to 35 years of age who will not be using any other form of contraception will receive relugolix combination therapy orally once daily (QD) for up to 1 year (ie, 13 consecutive 28-day treatment cycles) and will be assessed for the occurrence of pregnancy. To ensure the study is adequately powered for the assessment of the primary endpoint of the study, the PI, sample size reassessment will be performed periodically to assess the study power by evaluating the key assumptions used to determine whether the planned sample size of 900 participants needs to be adjusted based on the interim review of the trial data (see Section 9.2.3).

After participants sign the informed consent form (ICF), their eligibility will be assessed at Screening/Visit 1 (see Schedule of Activities; Table 1). After a thorough review of the participant's medical history, gynecological history including contraception, and use of prior medications, their height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including beta human chorionic gonadotropin (β-hCG) to rule out pregnancy. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial), if no normal result is available from an examination within 18 months prior to screening. Screening tests for the sexually transmitted diseases (STD) gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible for rescreening once they have received adequate treatment for the identified STD (see Section 8.1.2).

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 2, the timing of which depends on contraceptive status at screening and the need for washout of other contraceptive therapies. Continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an electronic diary (eDiary), which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of

the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. Home pregnancy tests will be provided for assessment prior to each cycle as required by the study and as needed during the cycle.

If Visit 2 occurs within 3 days of the onset of menses for participants not using any contraceptive method or using barrier contraception, or within the appropriate window for participants transitioning from another contraceptive method, the participant will begin her first treatment cycle of relugolix combination therapy by dosing with study medication at Visit 2. If the visit is not within the window to begin dosing, the participant will be dispensed the study intervention for initiation at home. When the participant reports the onset of the next menses in the eDiary or reaches the appropriate window to begin dosing if transitioning from another contraceptive method, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention. The first dose of study intervention will be confirmed by a phone visit. Once dosing of study intervention begins, the eDiary is organized by 28-day treatment cycles (ie, Cycle 1, 2, 3….), which are successive periods of 28 consecutive days. The eDiary continues with daily questions related to the intake of study intervention. At the end of each 28-day treatment cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding treatment cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding treatment cycle. Each subsequent treatment cycle starts with the result of a home pregnancy test, which must be negative and must be entered in the eDiary for a participant to continue in the study.

Participants will return to the clinic in the first week after completion of Cycle 1 for Visit 3. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Other records in the eDiary will be assessed, including use of other forms of contraception, occurrence of sexual intercourse during the first cycle (recorded once, at the end of the cycle), results of home pregnancy tests (if applicable), and the result of the protocol-required home pregnancy test prior to the start of Cycle 2. The occurrence of adverse events and use of concomitant medication since the last visit will be assessed. Body weight and vital signs will be measured. Study medication will be dispensed. Approximately 6 weeks after Visit 3, a telephone contact will be made (Phone 3; see Table 1), focusing on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable.

On-treatment site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur in the first week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively. Approximately 6 weeks following each on-treatment site visit, the participant will be contacted by telephone (Phone 4, Phone 5, and Phone 6). The site visits will have the same assessments described for Visit 3 above. Blood samples for liver tests will be collected at site Visit 5. The telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last

on-treatment visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

Fourteen days after completion of Cycle 13, or after early discontinuation of treatment, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on-treatment visits will be repeated, and final status assessed. In addition, physical, gynecological, and breast examinations will be conducted, and blood samples will be obtained for liver tests and β-hCG to determine pregnancy. Post-treatment contraception will be discussed and any remaining study medication and the eDiary will be collected.

Any participant who becomes pregnant during the study or is pregnant at the follow-up/EOT visit will undergo transvaginal ultrasound evaluation to determine gestational age and the estimated date of delivery. Pregnancies will be followed to outcome.

4.2. Scientific Rationale for Study Design

This is an open-label, single-arm, phase 3 study designed to demonstrate the contraceptive efficacy of relugolix combination therapy. The primary objective is to assess the contraceptive efficacy of relugolix combination therapy in healthy women 18 to 35 years of age who are at risk for pregnancy, as expressed by the At-Risk PI in the restricted intent-to-treat (rITT) population, based on the number of on-treatment pregnancies occurring during cycles without use of any contraceptive method other than relugolix contraceptive therapy and with confirmed vaginal intercourse. Study intervention will be self-administered during 13 consecutive 28-day treatment courses (“cycles”) for a total duration of 52 weeks.

To demonstrate the intrinsic contraceptive efficacy of relugolix combination therapy, a study population of women without impaired fertility is considered adequate (ie, women without gynecological conditions such as endometriosis or uterine fibroids, who have regular menstrual cycles, and who are in the optimum age range for conception [ie, between 18 to 35 years of age]). To support a proper assessment, women participating in this study should be sexually active with men and should agree to abstain from using other forms of contraception during the study.

Participants will visit the study site approximately every 12 weeks for safety evaluations, which include review of adverse events, eDiary, and concomitant medications, and collection of weight, vital signs (blood pressure, heart rate), and urine pregnancy test. Clinical laboratory evaluations will occur at Visit 5 and 7. The study eligibility criteria were designed to minimize risk to participants and rules for evaluation of liver test abnormalities, consistent with FDA guidance (FDA 2009), have been incorporated into the protocol.

4.3. Justification for Dose

The relugolix combination therapy doses of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg were selected for this study as they are the proposed clinical doses in women with heavy menstrual bleeding associated with uterine fibroids and pain associated with endometriosis.

In replicate pivotal phase 3 trials, within each of the indications studied, a 40-mg dose of relugolix combined with E2 1 mg and NETA 0.5 mg resulted in marked decrease in the heavy menstrual bleeding associated with uterine fibroids in a majority of women and a decrease in pelvic pain associated with endometriosis, respectively. Across the development programs, the

combination of relugolix with E2 and NETA at the selected doses demonstrated maintenance of BMD and prevented vasomotor symptoms associated with a hypoestrogenic state, without the risk of endometrial hyperplasia associated with unopposed estrogen. Across all studies, relugolix combination therapy was generally well tolerated in most participants, with an overall low rate of discontinuation due to adverse events. On the basis of the favorable benefit-risk profile observed in each indication, Myovant intends to commercialize relugolix combination therapy for the treatment of heavy menstrual bleeding associated with uterine fibroids and for pain associated with endometriosis.

In a study evaluating the effects of relugolix combination therapy on ovarian activity in healthy premenopausal women (MVT-601-046), relugolix combination therapy demonstrated inhibition of ovulation, as determined by Hoogland-Skouby score, in 100% of women receiving relugolix combination therapy during the entire 84-day treatment period. Therefore, these same doses are expected to be effective in preventing pregnancy.

4.4. End of Study Definition

A participant is considered to have completed the study if she has completed 13 28-day treatment cycles and the follow-up/end-of-treatment (EOT) visit (Visit 7), as shown in the Schedule of Activities (see Table 1).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Inclusion Criteria

A participant is eligible to be included in the study only if she meets all of the following criteria:

1. Has provided written informed consent for the trial;
2. Is a premenopausal woman, 18 to 35 years of age (inclusive);
3. Is at risk of pregnancy (ie, having heterosexual vaginal intercourse at least once per month with a partner who is not known to be subfertile or infertile) and is seeking contraception;
4. Has normal, regular menstrual cycles that are between 21 and 35 days in duration;
5. Has a negative serum pregnancy test result at Visit 1 and a negative urine pregnancy test result at Visit 2;
6. Is willing to use the investigational product as the sole method of contraception for 13 consecutive 28-day treatment cycles and does not intend to use any other form of contraception (eg, condoms, except when specified per protocol) from Visit 2 through the end of study participation;

7. Has good physical and mental health, based on medical, surgical, and gynecological history; physical, gynecological, and breast examinations; clinical laboratory test results; and vital sign measurements;
8. Has body mass index (BMI) ≥ 18 kg/m^2;
9. Is willing and able to fulfill the requirements of the protocol, especially daily use of the eDiary.

5.2. Exclusion Criteria

A participant is not eligible to be included in the study if she meets any of the following criteria:

Cardiovascular Risks and Disorders

1. Has presence or history of a venous thromboembolic event (VTE) (eg, deep vein thrombosis, pulmonary embolism), an arterial thrombotic or thromboembolic event (ATE) (eg, myocardial infarction, stroke, or peripheral arterial), or a transient ischemic attack, angina pectoris, or claudication;
2. Has a higher risk of VTE due to prolonged immobilization (eg, due to trauma, surgery, or other illness markedly limiting mobility) within 2 weeks prior to screening; plans for surgery requiring prolonged immobilization during the study; has a hereditary or acquired predisposition to or elevated risk for venous or arterial thrombosis, such as activated protein C resistance, antithrombin III deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, or antiphospholipid antibodies (eg, anticardiolipin antibodies, lupus anticoagulant); or has thrombogenic cardiac valve or rhythm abnormalities of the heart associated with thromboembolism (eg, atrial fibrillation);

   Note: Routine screening through laboratory tests for thrombophilia is not required. Exclusion from participation is based on reported medical history.
3. Has uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on two repeat measures at least 15 minutes apart at Visit 1 or Visit 2;
4. Has hypotension, as indicated by systolic blood pressure < 84 mmHg on two 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;
5. Has a history of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, torsades de pointes, Mobitz II second- or third-degree heart block without a permanent pacemaker in place, or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute [bpm]);
6. Has a history of migraine with aura or focal neurological symptoms;
7. Has diabetes mellitus with inadequate control (hemoglobin [Hb]A1C > 8%), end-organ involvement (eg, nephropathy, retinopathy, neuropathy, or vascular involvement) or has had diabetes for > 20 years duration;
8. Has multiple cardiovascular risk factors, such as obesity (BMI > 30 kg/m^2), inadequately controlled hypertension, use of tobacco/nicotine products, or inadequately controlled

diabetes, that together pose an unacceptable risk for a trial participant in the investigator's opinion. The investigator should consider the severity of each risk factor in determining whether trial participation is appropriate;

Note: The specific reasons for exclusion should be documented in the eCRF.

Gastrointestinal/Hepatobiliary Disorders

9. Has a history of pancreatitis associated with severe hypertriglyceridemia;
10. Has clinically significant liver disease, including active viral hepatitis or cirrhosis. Participants with a prior history of liver disease that is now inactive or has been successfully treated may be enrolled if liver function values (AST, ALT, total bilirubin) have been normal for the past year and are within the normal range (per central laboratory) at Visit 1. At the investigator's discretion, liver function testing may be repeated once prior to allocation of treatment if results are inconsistent with the participant's clinical status or recent laboratory results.

Note: Use of the same laboratory is recommended for repeat testing.

Laboratory Abnormalities During Screening

11. Has any of the following laboratory values:
    a. ALT or AST > 2.0 × upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 × ULN (or total bilirubin > 2.0 × ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Creatinine clearance < 60 mL/min by the Cockcroft-Gault formula
    c. Fasting triglycerides > 150 mg/dL;
    d. High-density lipoprotein level < 50 mg/dL.
12. Has any clinically relevant abnormal laboratory result at screening, as assessed by the investigator.

Gynecologic Conditions

13. Has a known history of infertility or sub-fertility;
14. Has gonorrhea, chlamydia, trichomoniasis, or symptomatic vaginitis/cervicitis. A participant may be rescreened 3 weeks after completing treatment for these conditions;
15. Has an abnormal cervical cytology or positive high-risk human papilloma virus (HPV) test result at screening or documented within 3 years of screening, (ie, atypical squamous cells of undetermined significance [ASCUS] with high-risk HPV positive, low-grade squamous intraepithelial lesion [LSIL] with high-risk HPV positive, high-grade squamous intraepithelial lesion [HSIL], atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion [ASC-H], squamous cell carcinoma, adenocarcinoma, atypical glandular cells of undetermined significance [AGUS], atypical glandular cells [AGC] neoplastic, or adenocarcinoma in situ [AIS]);

    Note: Cervical cancer screening within 18 months of trial entry is required for participants 21 years of age or older (or who will become 21 years old during the trial). Regardless of age, if a participant has had a cervical smear or test for high-risk strains of

HPV (ie, high-risk HPV test) performed within the last 3 years, the result must have been normal.

16. Within the past 6 months, has had undiagnosed (unexplained) abnormal vaginal bleeding or any abnormal bleeding that is expected to recur during the trial (eg, bleeding from cervical polyp, recurrent bleeding after intercourse).

Other Conditions/Disorders

17. Has a serious contraindication to pregnancy (eg, a medical condition or use of chronic medication such as isotretinoin or thalidomide);
18. Has known HIV infection or high risk of contracting HIV (eg, has multiple sexual partners, intravenous drug use in participant or partner);
19. Has a history of malignancy ≤ 5 years prior to signing informed consent form (ICF), except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer. Participants with a history or presence of liver tumors (benign or malignant) or sex steroid–influenced malignancies (eg, of the genital organs or breasts) are excluded, regardless of the interval since the history of the malignancy;
20. Has a current psychiatric disorder that would, in the investigator or medical monitor's opinion, impair the ability of the participant to participate in the study or would impair interpretation of their data. Participants 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 or mental health professional's judgement, 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;
21. Has any disease that may worsen under hormonal treatment, such as known gall bladder disease or a hepatic hemangioma;
22. Has had a known anaphylactic reaction, angioedema, or hypersensitivity to the investigational product or its excipients;
23. Has a history (current or within the past 2 years) of drug or alcohol abuse or dependence;
24. Has a history or current evidence of any condition, therapy, or other circumstance that in the opinion of the investigator or the medical monitor might expose the participant to risk through participating in the trial, confound the results of the trial, or interfere with participation for the full duration of the trial.

Recent or Current Pregnancy

25. Has a known or suspected pregnancy;
26. Has not had at least two menstrual cycles or has not completed two 28-day cycles of a hormonal contraceptive (pill, patch, or ring) following a recent pregnancy;
27. Is breastfeeding;

    Note: If recently stopped breastfeeding, must have resumed menstruation and must have had at least two normal menstrual cycles.

Concomitant and Recent Medications/Devices

28. Has used an investigational drug and/or has participated in any other clinical trial prior to Visit 2 within the past 30 days or within 5 half-lives (whichever is longer);
29. Is currently using an intrauterine device, intrauterine system, or contraceptive implant;
30. Is currently using a contraceptive method or other prohibited medication as detailed in Section 6.5.1 (suitable exclusionary window periods for these medications are also described therein).

Miscellaneous

31. Is part of the investigational site or sponsor staff directly involved with this study or has an immediate family member (eg, spouse, parent, legal guardian, sibling, or child) who is.

5.3. Lifestyle Considerations

No restrictions are required for treatment with relugolix combination therapy.

5.4. Screen Failures

Participants who consent to participate in the clinical study but are not subsequently entered in the study are considered to have had a screen failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any serious adverse event.

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Note: the study intervention in this study is relugolix combination therapy, also referred to as either relugolix combination therapy or study drug.

6.1. Study Intervention(s) Administered

Fixed-dose combination (FDC) tablets, each consisting of relugolix 40 mg, E2 1 mg, and NETA 0.5 mg will be supplied as immediate-release, yellow, film-coated tablets. In addition to the three active pharmaceutical ingredients, the core tablet formulation consists of compendial grade excipients including mannitol, lactose monohydrate, sodium starch glycolate, hydroxypropyl cellulose, and magnesium stearate.

The study intervention is presented in Table 4.

Table 4: Study MVT-601-050 Study Intervention

Intervention Name	**Relugolix Combination Therapy**
Type	Drug
Dose Formulation	Round film-coated yellow tablet
Unit Dose Strength	FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg)
Dosage Level(s)	Single FDC tablet (relugolix 40 mg/E2 1 mg/NETA 0.5 mg) QD
Route of Administration	Oral
Use	Experimental
IMP/NIMP	IMP
Sourcing	Provided centrally by the sponsor or locally by the trial site, subsidiary, or designee
Packaging and Labeling	Study intervention will be provided in a blister or bottle. Each will be labeled as required per US requirements.

Abbreviations: E2 = estradiol; FDC= fixed-dose combination; IMP = investigational medicinal product; NETA = norethindrone acetate; NIMP = non-investigational medicinal product; QD = once daily; US = United States.

6.2. Preparation/Handling/Storage/Accountability

Relugolix/E2/NETA (40 mg/1 mg/0.5 mg) FDC tablets are supplied to the study site in a container with 28 tablets. The FDC tablets are packed in either blisters cards or in a high-density polyethylene bottle. The FDC tablets should be stored in the original closed blister or bottle.

All study participants will take study intervention comprising one tablet daily at approximately the same time, 1 hour before or 2 hours after a meal.

If a dose is missed, instructions are as follows:

- If a dose is missed and the error is recognized on the same calendar day, the study intervention should be taken as soon as possible, and then regular dosing should be resumed the next calendar day at the usual time.
- If the missed dose is not recognized until the next calendar day (one missed dose), the dose intended for that calendar day should be taken as soon as possible, and regular dosing should be resumed the following day at the usual time.
- If 2 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time.
- If 3 to 6 consecutive doses are missed, a dose should be taken as soon as possible after the error is recognized, and regular dosing should be resumed the following day at the usual time. Back-up contraception should be used for 7 days.
- If 7 or more consecutive days are missed, the participant should begin using back-up contraception immediately and should be seen for an unscheduled visit. The medical monitor should be contacted.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all study drug received and that any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study intervention will be provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-arm study. Although participants and investigators are not blinded to the study treatment or the study outcome (pregnancy), bias is limited because the diagnosis of pregnancy is an objective measure.

6.4. Study Intervention Compliance

Study intervention will be self-administered during 13 consecutive 28-day treatment courses ("cycles"), for a total duration of 52 weeks (364 days). Participants should complete their eDiary each day on study and should bring all remaining study intervention and all used study intervention packages to each study visit. Compliance with daily intake of study intervention will be assessed based on drug accountability and records in the eDiary. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

A record of the number of tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for dose interruptions will also be recorded in the eCRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving or receives from the signing of the ICF through the end of the study must be recorded along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Medications

Table 5 provides examples of prohibited drug categories and windows of exclusion prior to screening; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding participant use of a particular drug or drug class.

Table 5: Study MVT-601-050 Prohibited Medications and Windows of Exclusion Prior to Screening

Drug Class and Effect	Examples	Window/Comments
Strong P-glycoprotein Inhibitors	amiodarone carvedilol[f] clarithromycin[a] cobicistat[e] cyclosporine[b] dronedarone erythromycin[a] gentamicin glecaprevir/pibrentasvir indinavir itraconazole[d] ketoconazole[d] lapatinib propafenone quinidine ranolazine ritonavir sofosbuvir/velpatasvir/voxilaprevir tetracycline verapamil[c] vemurafenib	2 weeks For participants requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study intervention administration during this period.
Combined P-glycoprotein and Strong CYP3A Inducers	carbamazepine lumacaftor mitotane phenobarbital phenytoin rifampin rifapentine St. John's wort	2 weeks
Hormonal Contraceptive pills, patches, and vaginal rings	combined or progestin-only Nuva Ring	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3
Long-acting injectable hormonal contraceptives	depot medroxyprogesterone acetate	9 months

Drug Class and Effect	Examples	Window/Comments
Progestin implants and intrauterine devices	Nexplanon Mirena Paragard	Must be discontinued prior to the first dose of study intervention as per Section 8.1.3
GnRH Analogues	leuprolide acetate injection, such as leuprorelin or goserelin acetate injections	3 months (6 months for 3-month injections)
Anti-Androgens	danazol	4 months
Aromatase Inhibitors	anastrozole letrozole	4 months
Progestins	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3])
Estrogens	estradiol valerate conjugated estrogens ethinyl estradiol	2 months (except if taken as part of a hormonal contraceptive [see Section 8.1.3]; 6 months for depot subcutaneous or intramuscular injections)
Selective Estrogen Receptor Modulators	raloxifene bazedoxifene asofoxifene clomifene tamoxifen	2 months
Selective Progesterone Receptor Modulators	mifepristone ulipristal acetate	6 months

Abbreviation: GnRH = gonadotropin-releasing hormone.
a. Azithromycin and roxithromycin are allowed.
b. Tacrolimus is allowed.
c. Amlodipine felodipine, diltiazem, and nifedipine are allowed.
d. Fluconazole is allowed.
e. Integrase inhibitors are allowed.
f. Metoprolol and atenolol are permitted.

6.6. Dose Modification

The dose level of relugolix combination therapy cannot be modified because it is administered as a single daily tablet.

Participants 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. Back-up contraception should be advised, as appropriate.

Participants may subsequently be re-started on study intervention with the written approval of the sponsor (or designee).

6.7. Intervention After the End of the Study

Not applicable to study MVT-601-050.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Any adverse event that is intolerable to the participant 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 participant if dosing continued;
- If it is discovered after enrollment that a participant failed to meet protocol entry criteria and continued participation would pose an unacceptable risk to their health;
- If the following liver test abnormalities develop, study intervention should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until their laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 × ULN; or
  - ALT or AST > 5 × ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 × ULN in conjunction with elevated total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QTc corrected using Fridericia's formula (QTcF) prolongation of more than 500 msec on an electrocardiogram done as part of patient care outside of the study protocol;
- Participants who are, in the opinion of the investigator or medical monitor, grossly noncompliant with the protocol requirements. Gross noncompliance includes < 75% compliance with the study intervention over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive visits) with < 50% of the required number of eDiary entries. Investigators will follow-up with the participant to encourage compliance with study intervention or eDiary prior to discontinuing her from the study;
- If the participant becomes pregnant at any time after signing the ICF, she must be withdrawn immediately (see Section 8.3.5 for information on pregnancy reporting).

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. The medical monitor should be consulted in advance of withdrawal whenever possible.
- At the time of discontinuing from the study, an EOT visit should be conducted, if possible. See the Schedule of Activities (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Table 1). Guidelines to address study conduct related to restrictions arising from the novel coronavirus 2019 global pandemic are addressed in Appendix 7.

8.1. Efficacy Assessments

8.1.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time point as described in the Schedule of Activities (see Table 1). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

8.1.2. Screening Period

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, cervical cancer screening) and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (see Table 1).

Prior to conducting any screening procedures, participants will be given a full description of the nature and purpose of the study and will be required to provide written informed consent. The investigator or a designated, medically qualified member of the site staff will interview potential participants and establish their eligibility for inclusion. Potential participants will be screened according to the inclusion and exclusion criteria (Section 5.1 and Section 5.2, respectively).

The participant's medical history, gynecological history including contraception, and use of prior medications will be reviewed. Menstrual history will be assessed to ensure the participant has a history of regular menstrual cycles every 21 to 35 days when not using hormonal contraception. If the menstrual cycle duration observed during the screening period does not meet eligibility criteria, screening may be extended with approval of the medical monitor. The participant's height, weight, and vital signs will be measured and a physical, gynecological, and breast examination will be performed. Blood samples will be obtained to assess safety parameters of hematology and blood chemistry, including β-hCG to rule out pregnancy. Cervical cancer screening will be performed in participants 21 years of age or older (or who will become 21 years old during the trial) if no normal result is available from an examination within 18 months prior to screening. Screening tests for the STDs gonorrhea and chlamydia will be conducted. Participants with positive results will not be allowed to continue but may be eligible to continue screening once they have received adequate treatment for the identified sexually transmitted disease and if the investigator determines the participant is not at high risk for reinfection (eg, because of multiple sex partners or an untreated partner). If the screening period

is extended by more than 6 weeks for any reason, screening laboratories (chemistry and hematology) should be repeated prior to administration of the first dose of study intervention.

8.1.2.1. Rescreening

Participants who fail screening may be rescreened with approval of the medical monitor. Participants undergoing rescreening will sign a new ICF and will be issued a new screening number.

8.1.2.2. 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. Other procedures, including cervical cytology, can be retested once without the permission of the medical monitor if necessary due to technical or logistical issues, such as an inadequate sample. Further retesting or retesting for other reasons requires the approval of the medical monitor.

8.1.3. Treatment Allocation

Participants who meet all eligibility criteria, including laboratory test and cervical cytology results, will return for Visit 2, the timing of which depends on contraceptive status at screening. All use of contraceptives must be discontinued prior to Visit 2.

At Visit 2, continued compliance with the eligibility criteria and the occurrence of adverse events after screening will be assessed, and applicable updates in medication use and history will be captured. Body weight and vital signs will be measured to determine baseline values. A urine pregnancy test will be performed to confirm that the participant is not pregnant. Participants will then receive an eDiary, which is a pivotal tool in the assessment of the primary and several secondary efficacy endpoints, as well as for compliance. Eligible participants will be instructed on the correct use of the eDiary and the importance of daily completion of the eDiary questionnaire. The ability to use the eDiary correctly is a prerequisite for participation. Finally, study medication will be dispensed together with instructions for administration and back-up contraception, if applicable. The first dose of study intervention will be administered on site at the time of Visit 2 or at home as described below. If dosing does not occur during Visit 2, the day of first dose (Day 1) will be confirmed by phone contact. Home pregnancy tests will be provided for assessment prior to each 28-day treatment cycle as required by the study and as needed during the cycle.

8.1.3.1. Prior Use of Hormonal Contraception, Implants, or Devices

For participants with prior use of hormonal contraception or implantable devices, the first dose of study intervention will be administered at Visit 2.

If the participant is transitioning from combined hormonal contraceptive pills, patches, or rings, she may schedule Visit 2 on the day she would normally initiate a new contraceptive cycle. If the visit cannot be scheduled on that day, it may be scheduled during the last 7 days of the method treatment cycle. Visit 2 procedures will be conducted at the site and the participant will be given the eDiary with instructions for use. On the day she would normally initiate a new

contraceptive cycle, she will be prompted by the eDiary to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

If the participant is transitioning from progestin-only pills she must schedule Visit 2 the day after completing treatment and use a back-up method for the first 7 days of relugolix combination therapy.

If the participant is transitioning from a contraceptive implant or intrauterine device, she must schedule Visit 2 the day the implant or device is removed and use a back-up method for the first 7 days of relugolix combination therapy. Note that only participants who have requested removal of their implant or intrauterine device for reasons unrelated to the purpose of enrollment may be considered for participation.

Participants using long-acting injectable contraceptive methods are not eligible to screen for the study until 9 months following their last dose.

8.1.3.2. No Prior Contraceptive Use or Use of Barrier Methods

If the participant was not using any prior contraceptive method or was using barrier contraception (diaphragm, cervical cap, male condom, female condom, or spermicidal foam, sponges, and film), she may schedule Visit 2 within 3 days of the onset of menses and the first dose of study intervention will be administered the day of the visit. If the visit cannot be reliably scheduled within the window to begin dosing, the visit should be scheduled prior to the onset of menses. Visit 2 procedures will be conducted, and the participant will begin daily eDiary entries related to the onset of menses. When the participant reports the onset of the next menses in the eDiary, she will be prompted to perform a home urine pregnancy test. With entry of a negative urine pregnancy test result, the eDiary will instruct the participant to take and record the first dose of study intervention.

8.1.4. Treatment Period

Once dosing of study intervention has been initiated, participants will take their study intervention QD. Dosing of study intervention will be organized by “cycles” of successive periods of 28 days. Participants will self-administer study intervention through the completion of Cycle 13. Participants will record compliance with study intervention dosing daily in their eDiary. At the end of each cycle, the eDiary asks two additional questions, both of which are pivotal for the assessment of the primary endpoint. The first question is whether sexual intercourse has occurred during the preceding cycle, and the second question is whether any form of contraception (including emergency contraception) was used during the preceding cycle. Each subsequent cycle starts with the result of a home pregnancy test, which must be negative and entered in the eDiary for the participant to continue the study.

8.1.4.1. Site Visits

Participants will return to the clinic the first week after completion of Cycle 1 for Visit 3.

Subsequent site visits (Visit 4, Visit 5, and Visit 6) are planned at intervals of 12 weeks (3 cycles), to occur 1 week after completion of Cycle 4, Cycle 7, and Cycle 10, respectively.

Study medication will be dispensed at each visit. See the Schedule of Activities (see Table 1) for assessments required for each visit.

8.1.4.2. Telephone Visits

Approximately 6 weeks following each site visit, the participant will be contacted by telephone (Phone 3, Phone 4, Phone 5, and Phone 6). The first telephone contact will occur approximately 6 weeks after Visit 3. Telephone contacts will focus on the assessment of adverse events and concomitant medications, compliance with daily intake of study intervention, compliance with daily completion of the eDiary, pregnancy risk, and logistical issues, as applicable. The last visit (Visit 6) and telephone contact (Phone 6) will also include discussions of contraception after study intervention is completed.

8.1.4.3. 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 participant'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 (hematology and chemistry), urine or serum pregnancy testing, study intervention compliance, and dispensation of study intervention may be conducted as needed. Consult with the medical monitor, if needed, to discuss unscheduled visit testing.

8.1.5. Post-Treatment Period

8.1.5.1. End-of-Treatment Visit

Two weeks after completion of Cycle 13, participants will return to the clinic for the follow-up/EOT visit (Visit 7). All assessments done at on-treatment visits will be repeated, and final status assessed; in addition, physical, gynecological, and breast examinations will be conducted. Blood samples will be obtained for liver tests and β-hCG to determine pregnancy. Post-treatment contraception will be discussed. Any remaining study medication and the eDiary will be collected.

8.1.5.2. Early Termination Visit

If the participant does not complete the study for any reason (including investigator discretion), the reason and circumstances for the participant's early termination must be fully documented. If possible, the assessments specified for the follow-up/EOT visit (Visit 7) should be performed. The medical monitor should be consulted in advance of withdrawal whenever possible. Participants who are withdrawn from the study may not be re-enrolled.

8.1.5.3. Pregnancy Visit

If a participant becomes pregnant during the study, the site must discontinue the participant from study intervention immediately and have her return for a visit (see Table 1). In addition to the follow-up/EOT procedures the participant will undergo the following diagnostic procedures:

- Quantitative serum pregnancy test (unless pregnancy already confirmed by transvaginal ultrasound);
- Transvaginal ultrasonography to determine gestational age/estimated date of delivery (EDD).

8.1.6. Efficacy Evaluations

Planned time points for efficacy assessments are provided in the Schedule of Activities (see Table 1).

8.1.6.1. Pregnancy Testing

The contraceptive efficacy of relugolix combination therapy will be evaluated using the number of on-treatment pregnancies. On-treatment pregnancies are pregnancies with an estimated conception date (ECD) between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Pregnancy testing is conducted per the Schedule of Activities (see Table 1) as follows:

- A serum β-hCG pregnancy test is performed at Visit 1 and Visit 7. Serum testing is also performed during the study if a pregnancy is suspected or to confirm a pregnancy reported by a participant (unless already confirmed by transvaginal ultrasound). A urine pregnancy test is performed at all site visits after screening and as needed;
- A home urine pregnancy test performed by the participant is required prior to the start of each cycle, and the result must be negative to continue on study. Any positive pregnancy test should be confirmed by a serum β-hCG pregnancy test (and transvaginal ultrasound when applicable).

8.1.6.2. Participant eDiary

All participants enrolled in the study will be provided a device with an application for a participant eDiary at Visit 2, along with detailed instructions for its use (see Appendix 6). Participants will complete daily eDiary entries including compliance with study intervention dosing, occurrence of sexual intercourse, use of back-up contraception, and home urine pregnancy test results. The eDiary data will be reviewed by the study staff on an ongoing basis and at specified timepoints as noted in the Schedule of Activities (see Table 1).

8.2. Safety Assessments

Study assessments of safety include adverse events, physical examinations, vital signs (and weight), and clinical laboratory tests. Planned time points for all safety assessments are provided in the Schedule of Activities (see Table 1).

8.2.1. Physical Examinations

A complete physical examination, including gynecological and breast examination, will be conducted at Visit 1 and the follow-up/EOT visit (Visit 7). The examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes,

gastrointestinal, skeletal, and neurological systems. Height and weight will also be measured and recorded.

All other physical examinations should focus on signs and symptoms reported by the participant to assess for clinically significant changes from the baseline assessment.

The gynecologic examinations at screening will include testing for gonorrhea and chlamydia. Cervical cytology test must be conducted for participants 21 years or older (or who will become 21 years old during the trial) without an available test result from within 18 months years prior to the Screening Visit and submitted to the central laboratory. A repeat test should be performed for inadequate specimen and submitted to the central laboratory.

A bilateral breast examination will be performed at the time of the gynecologic examination.

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

8.2.2. Vital Signs

Vital signs including heart rate and systolic and diastolic blood pressure will be assessed. Vital signs will be measured with the participant in a seated position and should be preceded by at least 5 minutes of rest with the participant in a quiet setting without distractions (eg, television, cell phones). Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3. Electrocardiograms

Electrocardiograms are not routinely collected during the study and are to be performed per general clinical safety assessment, as applicable.

8.2.4. Clinical Laboratory Tests

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (see Table 1) for timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the eCRF. Laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within two weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the medical monitor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (see Table 1).

If laboratory values from non–protocol -specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, serious adverse event, adverse event, or discontinuation of study intervention), then the results must be recorded in the eCRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

There will be ongoing monitoring of adverse events associated with mood disorders (see also Section 2.3.1).

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1. Time Period and Frequency of Collecting Adverse Event and Serious Adverse Event Information

All adverse events and serious adverse events will be collected from signing of the ICF until the safety follow-up/EOT visit (Visit 7) approximately 14 days after the last dose of study intervention. 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 intervention.

All serious adverse events will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event after conclusion of the study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse reports are provided in Appendix 3.

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 participant is the preferred method to inquire about adverse event occurrences.

The participant's eDiary entries 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 this instrument, proper follow-up with the participant 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.

8.3.3. Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All serious adverse events and adverse events of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up as defined in Section 7.3.

At the conclusion of the study, the investigator and medical monitor will assess unresolved adverse events and determine if additional follow-up is warranted. Further information on follow-up procedures is provided in Appendix 3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.

For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (eg, summary or listing of serious adverse events) from the sponsor will review and then file it along with the [Investigator's Brochure] and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy Reporting

Details of all pregnancies will be collected after the start of study intervention and until the follow-up visit/EOT (Visit 7) (see Schedule of Activities, Table 1).

If a pregnancy is reported, study intervention should be withdrawn immediately and the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

8.3.6. Adverse Events of Clinical Interest

Adverse events of clinical interest in this study are defined as any increase in ALT or AST $\geq 3 \times$ 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 safety report form within 24 hours of the study site personnel's knowledge of the event, even if the event does not meet serious adverse event criteria. Additional instructions for evaluating participants with an increase in ALT or AST $\geq 3 \times$ ULN may be found in Appendix 5.

8.3.6.1. Criteria for Temporary Withholding of Study Intervention 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 intervention should be immediately withheld with appropriate clinical follow-up (including repeat laboratory tests, until the participant's laboratory profile has returned to normal/baseline status), and the event reported per Section 8.3.6 and as a serious adverse event if serious adverse event criteria met, including the underlying diagnosis, as available:

- ALT or AST > 8 × ULN; or
- ALT or AST > 5 × ULN and persists for more than 2 weeks; or
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5; or
- ALT or AST > 3 × 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.

8.3.6.2. Criteria for Permanent Discontinuation of Study Intervention in Association with Liver Test Abnormalities

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

1. ALT or AST increases to ≥ 3 × ULN; AND
2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × 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 intervention treatment should be withheld or permanently discontinued as appropriate for the safety of the participant.

8.3.7. Adverse Events Related to Menstrual Bleeding

To ensure consistent reporting, the terms below should be used when participants report alterations from their usual menstrual bleeding pattern that meet adverse event reporting criteria. Select the term that most closely reflects both the volume of the menstrual flow and the frequency/duration/regularity of the bleeding episodes.

- Amenorrhea: Absence of menstrual bleeding
- Spotting Vaginal: Spotting regardless of the frequency/duration/regularity
- Oligomenorrhea: Infrequent bleeding/light or normal volume
- Polymenorrhea: Frequent bleeding/light or normal volume
- Menorrhagia: infrequent or regular frequency bleeding/ heavy volume OR prolonged bleeding regardless of flow volume
- Hypomenorrhea: regular frequency/light volume
- Metrorrhagia: irregular frequency/light or normal volume
- Menometrorrhagia: irregular bleeding/heavy volume

8.4. Treatment of Overdose

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

For this study, the protocol-specified dose of relugolix combination therapy is one tablet once daily. 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 participant for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a safety report form according to Appendix 3 whether or not the overdose is associated with an adverse event;
- Document the quantity of the excess dose as well as the duration of the overdosing in the Overdose eCRF page.

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

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not assessed in this study.

8.10. Health Economics/ Medical Resource Utilization

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no hypothesis associated with the primary endpoint.

9.2. Sample Size Determination

9.2.1. Assumptions

To support the primary contraceptive efficacy analysis, the sample size of this trial has been set to attain at least 5,000 treatment cycles at-risk for pregnancy in participants 18 to 35 years of age at the time of enrollment. In calculating the sample size, the following assumptions were made:

- The study has a duration of 13 28-day cycles;
- 45% of participants will discontinue the trial;
- Discontinuers will, on average, contribute 4 cycles of exposure;
- 30% of cycles will not be at-risk;
- Pearl Index ~ 2.0.

9.2.2. Power Calculations

The sample size and power calculations were based on the simulation work using the above assumptions. The methodology described by (Benda et al. 2004) was used for calculating the 95% confidence interval (CI) for the PI with the assumption of a Poisson model for number of on-treatment pregnancies. In the Poisson model, a Poisson distributed random variable X is assumed with parameter $\theta = 100\lambda T$ where λ is the pregnancy rate per year and T is the total exposure time in 100-woman years. X represents the number of on-treatment pregnancies occurring during a total exposure time of 100T woman-years. The PI is given by $\rho = \theta/T$ which is the expected number of pregnancies within 100-woman years (or 1300 28-day cycles). Based on this model, a 95% CI was derived for each simulation. Power (probability of success) was estimated as the proportion of the simulated 95% CIs meeting the criterion that the upper bound of the 95% CI is less than 5, consistent with FDA Guidance for Industry (FDA 2019).

With at least 5000 on-treatment cycles at-risk for pregnancy (~ 400 woman-years), the study will have approximately 90% power for the upper bound of the 95% two-sided CI for the PI to be below 5.

Approximately 900 participants must be enrolled to achieve at least 5000 at-risk cycles. Taking into account a screening failure rate of 15%, a total of approximately 1060 participants will be screened.

The number of at-risk cycles will be monitored, and enrollment will be adjusted to ensure that at least 5000 on-treatment at-risk cycles are achieved the end of the study.

Note: "Enrolled" is defined as a participant who has completed the informed consent process, completed screening procedures, and has been allocated to treatment. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

9.2.3. Sample Size Reassessment

To ensure that the trial is adequately powered for the evaluation of contraceptive efficacy measured by Pearl Index (PI), sample size reassessment will be performed periodically to check the key assumptions used for sample size calculations. In particular, the PI will be calculated from interim data to check the accuracy of the assumption (PI = 2) used for the initial sample size calculation. The planned sample size of 900 participants may be adjusted from the interim calculation to ensure the study is adequately powered to evaluate contraceptive efficacy. The detailed methodology for the sample size reassessment during the trial will be described in the statistical analysis plan.

9.3. Populations for Analyses

The analysis populations are defined in Table 6.

Table 6: Study MVT-601-050 Analysis Populations

Analysis Population	Description
Enrolled	All participants who sign the ICF
Intent-to-Treat (ITT)	All participants who receive at least one dose of study intervention
Modified Intent-to-Treat (mITT)	The subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred
Per-Protocol (PP)	The subset of participants in the rITT population with at least one treatment cycle that is also without specific protocol deviations
Restricted Intent-to-Treat (rITT)	The subset of participants included in the ITT population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred

Abbreviations: ICF = informed consent form.

9.4. Statistical Analyses

A statistical analysis plan will describe the detailed statistical methods and analyses for this study. The statistical analysis plan will be finalized prior to database lock. This section provides a summary of the planned statistical analyses of the endpoints, including primary and key secondary endpoints.

9.4.1. General Considerations

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 participants. Categorical data will be summarized by counts and percentages.

The single, final analysis of all efficacy and safety data will occur after approximately 900 participants have enrolled and been followed for thirteen cycles, if not early terminated.

9.4.2. Evaluable Cycles and Pearl Index Definitions

Evaluable cycles are defined below and will contribute to the denominator for calculating each type of PI.

- At-Risk PI (primary efficacy endpoint): Cycles without use of any other contraceptive methods and with confirmed vaginal intercourse (At-Risk Cycles).
- Gross PI: On-treatment cycles.
- Modified At-Risk PI: Cycles without use of any other contraceptive methods regardless of occurrence of vaginal intercourse.
- Method Failure PI: At-Risk Cycles without major protocol deviations.

9.4.3. Primary Endpoint

The contraceptive efficacy of relugolix combination therapy will be assessed using the At-Risk PI, defined as the number of on-treatment pregnancies per 100 women-years of treatment:

$$\text{Pearl Index (PI)} = \frac{1300 \times (\text{number of on-treatment pregnancies})}{\text{number of 28-day at-risk cycles of treatment}}$$

There is no hypothesis associated with the primary endpoint. The primary contraceptive efficacy will be assessed by the point estimate of At-Risk PI and corresponding 95% CI. On-treatment pregnancies are pregnancies with an ECD between the first day of study intervention intake up to and including 7 days after the last intake of study intervention.

Transvaginal ultrasound will be the primary method for determining the timing of conception. From the ultrasound the EDD will be ascertained. The ECD will be calculated as:

$$\text{EDD} - 38 \text{ weeks} = \text{ECD}$$

If no transvaginal ultrasound is available, the ECD will be determined from one of the following (if available): EDD as entered into the obstetric record, date of last menses or β-hCG level.

The At-Risk PI will be calculated on the basis of cycles considered at-risk of pregnancy (ie, consecutive 28-day periods without use of any other contraceptive methods and with affirmed occurrence of vaginal intercourse. The numerator and denominator in the At-Risk PI calculation are slightly discrepant, in that the numerator will also include pregnancies with a conception date during cycles that were not considered at risk.

Estimation of the At-Risk PI, as the primary contraceptive efficacy analysis, will be conducted using an rITT population, defined as the subset of participants included in the intent-to-treat (ITT) population who have at least one at-risk treatment cycle or who have a treatment cycle (at-risk or not) in which a pregnancy has occurred . The At-Risk PI will be presented together with the two-sided 95% CI calculated based on a Poisson distribution (Benda et al. 2004).

9.4.4. Secondary Endpoints

Among all PIs thus calculated, the Gross PI and the Method Failure PI have numerator and denominators referring to exactly the same exposure. Similarly, the secondary PIs will be presented together with their two-sided 95% CIs with a Poisson distribution. Specifically:

- The Gross PI will be estimated using the ITT population, defined as participants 18 to 35 years of age at the time of enrollment who have entered the study and have at least one on-treatment cycle.
- The modified PI will be estimated using the modified ITT (mITT) population, defined as the subset of participants included in the ITT who have at least one treatment cycle without use of other contraceptive methods, or participants with a treatment cycle (at-risk or not) in which a pregnancy has occurred .
- The Method Failure PI will be estimated using the per protocol analysis population, defined as the subset of participants in the rITT population, with at least one treatment cycle that is also without specific protocol deviations. For calculation of the

Method Failure PI, only pregnancies with a conception date during at-risk cycles that were also per protocol are included in the numerator.

- Cumulative 1-year pregnancy rate will be calculated on each of the analysis populations by the Kaplan-Meier (KM) survival analysis. All participants will be followed until they either have an outcome of pregnancy or are censored at the time of their last follow-up. The unit of time in the KM analysis will be the cycle, with pregnancies recorded by cycle of conception. Unlike the PI calculations, cycles based on use of adjunctive contraception will not be excluded.

9.4.5. Tertiary/Exploratory Endpoint(s)

Not applicable.

9.4.6. Safety Endpoints

The analysis of safety endpoints will be conducted and summarized using the ITT population. Adverse event summaries will be based on treatment-emergent adverse events, unless otherwise specified. The treatment-emergent period will be defined as the period of time from the first dose date of study intervention through approximately 14 days following the last dose of study intervention. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, vital signs, and laboratory evaluations.

The severity of all adverse events will be evaluated by the investigator based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). All adverse events will be coded to preferred term and system organ class using MedDRA Version 23.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study intervention treatment, and severity. An adverse event reported more than once for a participant is counted once at the maximum severity or strongest relationship to study intervention treatment when calculating incidence.

Laboratory data consists of chemistry and hematology parameters. Only data collected by the central laboratory will be used to do the analyses. Tables summarizing values meeting predefined limits of change will be provided. The National Cancer Institute's CTCAE, will be used to categorize toxicity grade for laboratory parameters. 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 for each laboratory test.

Vital signs parameters will be listed and summarized by visit. The change from baseline for each post-baseline study visit will be presented for each parameter.

9.4.7. Other Analyses

Not applicable.

9.5. Interim Analyses

No formal interim analyses are planned for this study.

9.6. Data Monitoring Committee

This is an open-label single-arm study, and no Data Monitoring Committee will be convened. The safety of study participants will be closely monitored on an ongoing basis by Myovant Sciences representatives in close consultation with the Drug Safety and Pharmacovigilance Department. Issues identified will be addressed; this could involve, for example, amendments to the study protocol, and letters to investigators.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines;
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
  - Applicable laws and regulations.
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an institutional review board (IRB)/(independent ethics committee) IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
  - Notifying the IRB/IEC of serious adverse events or other significant safety findings as required by IRB/IEC procedures;
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Financial Disclosures

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants undergoing rescreening will sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Dissemination of Clinical Study Data

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

Data Quality Assurance

Documentation Accountability

- All participant data relating to the study will be recorded on printed or electronic case report form (CRF) unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the completion of the informed consent process by the first participant and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 2. CLINICAL LABORATORY TESTS

- All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the protocol Schedule of Activities (see Table 1).
- Laboratory requisition forms must be completed, and samples must be clearly labeled with the Participant 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 7.
- Investigators must document their review of each laboratory safety report.
- Local laboratory results are only required in the event that central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7: Study MVT-601-050 Protocol-Required Safety Laboratory Assessments

Chemistry	**Hematology**	**Other**
Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Liver tests: Bilirubin Total Alanine Aminotransferase Aspartate Aminotransferase Gamma-Glutamyl Transferase Alkaline phosphatase LDH	WBC Count WBC Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count RBC morphology	Serum Pregnancy Test (β-hCG) Urine Pregnancy Test Hemoglobin A1C
	Lipid Profile	**Hepatitis Serology**
	Total Cholesterol Low Density Lipoprotein High-Density Lipoprotein Triglycerides	Hepatitis A antibody Hepatitis B surface antigen Hepatitis B Core antibody Hepatitis C antibody

Abbreviations: β-hCG= beta human chorionic gonadotropin; LDH = lactic acid dehydrogenase; RBC = red blood cells; WBC = white blood cell.

APPENDIX 3. ADVERSE EVENTS DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP AND REPORTING

Definition of Adverse Event

Adverse Event Definition
• An adverse event is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events NOT Meeting the Adverse Event Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the adverse event. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of Serious Adverse Event

If an event is not an adverse event per definition above, then it cannot be a serious adverse event even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

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

a. Results in death

b. Is life-threatening

- The term 'life-threatening' in the definition of 'serious' refers to an event in which the 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient 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 disability/incapacity

- 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 with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgement should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include 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.

Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and/or Serious Adverse Event Recording

- When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant adverse event or serious adverse event information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or their representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the adverse event or serious adverse event.

Assessment of Intensity

The investigator will make an assessment of intensity for each adverse event and serious adverse event reported during the study according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). For terms not specified with the CTCAE, the criteria below should be used to determine the grade severity:

Severity 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

Note: An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of a serious adverse event, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each adverse event.
A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
The investigator will use clinical judgement to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each adverse event, the investigator **must** document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to PHV-Myovant@quintiles.com. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event to PHV-Myovant@quintiles.com.

The investigator may change his/her opinion of causality in light of follow-up information and send a Safety Report Form follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions are to be used for the relationship of the adverse event to study intervention:

- **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.

Follow-up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to PHV-Myovant@quintiles.com within 24 hours of receipt of the information.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to IQVIA RDS, Inc. via Paper CRF

- E-mail transmission of the Safety Report Form paper CRF is the preferred method to transmit this information to the global safety database.
- In rare circumstances and in the absence of e-mail or e-fax equipment, notification by telephone is acceptable with a copy of the Safety Report Form data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Safety Report Form within the designated reporting time frames.
- Contacts for serious adverse event reporting follow:

Using a Safety Report Form, all serious adverse events must be reported within 24 hours of the study site personnel's knowledge of the event, regardless of the investigator assessment of the relationship of the event to study intervention.

The contact information for submission of serious adverse events, adverse events of clinical interest, and events of overdose is available on the Safety Report Form and is as follows:

Site Location	E-mail (Primary Reporting Method)	Fax Number (Secondary Reporting Method)
All Regions	[redacted]	[redacted]

For questions regarding serious adverse event or adverse event of clinical interest reporting, please call:

- North/South America: [redacted]
- Regional toll-free phone and fax lines distributed separately.

The initial report should include:

- Study number (MVT-601-050)
- Site address and number
- Investigator name
- Participant ID number, sex, and age
- Details of study intervention 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 intervention

If the participant 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 intervention 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, stabilization, the event is otherwise explained, or the participant is lost to follow-up. All serious adverse events continuing at the completion of the study must be assessed or followed to determine outcome.

APPENDIX 4. COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the pregnancy report form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an adverse event or serious adverse event.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be a serious adverse event and will be reported as such.
- Any post-study pregnancy related serious adverse event considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of a serious adverse event through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention immediately and return for a Pregnancy visit as described in Section 8.1.5.3.

APPENDIX 5. LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Study intervention (relugolix combination therapy) should be withheld for any liver test abnormality listed in Section 8.3.6, 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 Table 8, and per the investigations in Table 9. If close monitoring is not possible, study intervention should be withheld even if the results do not meet the criteria for withholding in Section 8.3.6.

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

Table 8: Study MVT-601-050 Monitoring of Liver Tests for Potential Drug-Induced Liver Injury

Results	Frequency for Repeating Liver (ALT, AST, Bilirubin [Total and Direct]), Alkaline Phosphatase, and INR Tests
If ALT or AST ≥ 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 participant is asymptomatic	Frequency may decrease

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

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

Table 9: Study MVT-601-050 Investigations and 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 Table 8; • 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).

Abbreviations: CBC = complete blood count; INR = International normalized ratio.
Note: If the first follow-up test does not confirm the initial abnormal liver test results, review any additional follow-up monitoring with the medical monitor.

APPENDIX 6. PARTICIPANT DAILY EDIARY

Questions Pertaining to Study Intervention Initiation

- Participants who must wait for the onset of menses to begin study intervention (those who are not using any prior contraceptive method or who are using barrier contraception) will receive these questions:

Did you start your menstrual period today?
- □ No
- □ Yes
  - o If Yes, subject will be prompted to take a urine pregnancy test.

Please take a urine pregnancy test today and record the result:
- □ Negative (not pregnant)
  - Message: Please take your first dose of study intervention.
  - *Cycle 1 Questions will then follow.*
- □ Positive (pregnant)
  - Message: Do not take any study intervention and contact the site immediately.

- Participants who must wait for the day they would normally begin a new contraceptive cycle to begin study intervention (those who are transitioning from combined hormonal contraceptive pills, patches, or rings) will receive the following instruction:

Please take a urine pregnancy test today and record the result:
- □ Negative (not pregnant)
  - Message: Please take your first dose of study intervention.
  - *Cycle 1 Questions will then follow.*
- □ Positive (pregnant)
  - Message: Do not take any study intervention and contact the site immediately.

Questions for Cycle 1

Daily Questions:
Did you take your dose of study intervention today?
- □ Yes
  - o If Yes, please provide Time:
    HH:MM [AM/PM]
- □ No

Did you take your dose of study intervention while on an empty stomach at least 1 hour before or two hours after a meal?
- □ Yes
- □ No

Additional questions on the last day of the Cycle:
Did you have vaginal sexual intercourse at any time during this treatment cycle?
- □ Yes
- □ No

Did you use any other form of birth control in addition to the study intervention during this treatment cycle?

□ Yes
□ No

Questions for Cycle 2-13

Questions on Day 1 of Cycle:
Please take a urine pregnancy test today and record the result:

□ Negative (not pregnant)
Message: You may continue taking study intervention as scheduled.
□ Positive (pregnant)
Message: Discontinue study intervention and contact the site immediately.

Did you take your dose of study intervention today?

□ Yes
- If Yes, please provide Time:
  HH:MM [AM/PM]

□ No

Did you take your dose of study intervention while on an empty at least 1 hour before or two hours after a meal?

□ Yes
□ No

Daily Questions After Day 1 of Cycle:
Did you take your dose of study intervention today?

□ Yes
- If Yes, please provide Time:
  HH:MM [AM/PM]

□ No

Did you take your dose of study intervention while on an empty at least 1 hour before or two hours after a meal?

□ Yes
□ No

Additional questions on the last day of the Cycle:
Did you have vaginal sexual intercourse at any time during this 28-day treatment cycle?

□ Yes
□ No

Did you use any other form of birth control in addition to the study intervention during this treatment cycle?

□ Yes
□ No

Questions for Unscheduled Home Urine Pregnancy Tests

Please enter date of urine pregnancy test:

DD/MMM/YYYY

Please record the result of the unscheduled urine pregnancy test

□ Negative (not pregnant)
□ Positive (pregnant)
Message: Discontinue study intervention treatment and contact the site immediately.

APPENDIX 7. GUIDANCE FOR STUDY CONDUCT DURING THE COVID-19 PANDEMIC

The novel coronavirus 2019 (COVID-19) pandemic has impacted the conduct of clinical trials globally. Regional quarantine laws, travel restrictions, and site closures present challenges to normal study conduct and may lead to missed study visits or procedures or an interruption to a patient's study drug supply.

Myovant Sciences has thoroughly reviewed guidance documents from various country and regional regulatory agencies and has put mitigation plans in place to ensure that the safety of patients is maintained, the study continues to be conducted in compliance with Good Clinical Practice (GCP), and risks to the integrity of the study are minimized. These plans will remain in place through the duration of the COVID-19 pandemic.

Safety During the COVID-19 Pandemic

Protecting study patients, investigational site staff and clinical service providers involved in Myovant Sciences clinical studies from activities that may unnecessarily increase the risk of contracting COVID-19 is of utmost importance. Regulations and policies instituted for safety purposes during the COVID-19 pandemic at the institutional, local, country, and regional level should be adhered to.

Protocol Adherence

Wherever possible and safe, study visits and procedures must be performed as outlined in the protocol to ensure patient safety and to maintain the integrity and interpretability of the study data. While modifications to normal study conduct may, in some cases, be necessary and unavoidable, they must be documented and reported where in conflict with the study protocol and this guidance. Deviations from the protocol will be documented, but those resulting specifically from the COVID-19 pandemic will be marked as such. All deviations resulting from the COVID-19 pandemic will be summarized in the clinical study report.

Visit Schedules and Study Procedures

Local policies, institutional restrictions, and/or patient ability/willingness to make site visits may curtail the ability to adhere to the in-person, on-site visit schedule required by the protocol. Investigators at clinical sites should evaluate the appropriateness of an on-site study visit during the COVID-19 pandemic.

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, as close to the visit target date as possible, taking all measures to prevent contracting COVID-19.

- All protocol-required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, Investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.

- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the Myovant medical monitor for consultation as necessary.

If the clinical study site is closed or the patient is unable/unwilling to attend on-site study visits due to the COVID-19 pandemic, alternative methods for completing assessments (eg, phone contact or virtual visit) should be implemented.

- Investigators must assess and evaluate the patient's continued participation and dosing with limited safety assessment.
- At a minimum, investigational site staff should make every attempt to contact the patient via telephone when an expected visit is due or missed to assess for adverse events, document concomitant medications, and study drug dosing since the last study visit.
- If the safety blood draws cannot be performed through the central laboratory per protocol, the investigator may advise the patient to have blood drawn at a local laboratory if there is a safety concern. If two consecutive study visits are missed and the patient is unable to return to the site, the investigator should advise the patient to have protocol-specified safety labs completed at a local laboratory to assess for any safety concerns. In both cases, the local laboratory results should be documented in the eCRF.
- Investigational sites should report all serious adverse events, adverse events of clinical interest, overdose, and pregnancy that the patient reports during these calls within 24 hours of awareness.
- Patients should be reminded of the importance of taking study drug daily or of using back-up contraception if study drug is interrupted.
- Study patients should continue to complete their daily eDiary, even if they run out of study drug, and site staff should motivate them to do so.

Patients should have the contact details of the investigational site medical staff to report any medical issues, including adverse events they may experience in real time.

As soon as the study patients are able to return to the investigational site for an on-site visit, they should do so. The next scheduled visit should occur on the target date as per the Schedule of Activities (see Table 1).

Study Participant Study Drug Supply

If a regional lockdown, travel restrictions, or site closure is imminent due to the COVID-19 pandemic, sites are encouraged to dispense additional study drug at an expected study visit or request patients to return for an unscheduled visit for additional study drug dispensation so patients have sufficient supply until their next upcoming visit. Patients should be instructed to

contact the site to report any medical issues they may experience and site staff should communicate with the patients to determine if it is appropriate for the patient to continue dosing with study drug if/when in-person study visits are not possible.

For cases where study patients are unable to visit the investigational site to pick up study drug, a direct-to-patient delivery of study drug by site staff or shipment via contracted courier may be possible. Consent authorizing direct-to-patient supply will be obtained. Sites should defer to national guidance on how this will occur. Where permitted by national guidance, verbal consent will be taken via telephone or video call and noted in the patient's source file. Where required, by national guidance, this will be followed up with written consent during the next clinic visit. Every effort will be made to obtain the patient's written consent for direct-to-patient delivery prior to delivery or shipment, where this is required by national guidance.

In the event that none of the above are possible for participants to continue taking study medication, a patient may need to be discontinued per the study protocol. Such decisions will be made on a case-by-case basis in discussion with the investigator and medical monitor.

On-Site Study Monitoring Restrictions

In the event study monitors/clinical research associates are not allowed to travel and/or return to a clinical site to monitor and source document verify study data, Myovant has developed plans to ensure monitors:

- Remotely verify source documentation as much data as reasonably possible without burdening sites, if allowed by the study site and country regulations, focusing on pages key to the interpretability of the study and the safety of participants.
- Remotely monitor study data through cross checking of various systems housing patient data against what is captured in the eCRFs.

Additional guidance on conducting clinical trials during the COVID-19 pandemic may be found in the following documents released by Regional Health Authorities, which may be updated (updates supersede the versions listed here):

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated June 03, 2020);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (28 April 2020).

APPENDIX 8. ABBREVIATIONS

List of Abbreviations and Definition of Terms

Abbreviation	Definition
β-hCG	beta human chorionic gonadotropin
AGC	atypical glandular cell
AGUS	atypical glandular cells of undetermined significance
AIS	adenocarcinoma in situ
ALT	alanine aminotransferase
ASC-H	atypical squamous cells that cannot exclude high-grade squamous intraepithelial lesion
ASCUS	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
ATE	arterial thrombotic or thromboembolic event
BMD	bone mineral density
BMI	body mass index
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	novel coronavirus 2019
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
E2	estradiol
ECD	estimated conception date
eCRF	electronic case report form
EDD	estimated date of delivery
eDiary	electronic diary
EOT	end-of-treatment
FDA	Food and Drug Administration
FDC	fixed-dose combination (tablet)
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HIV	human immunodeficiency virus
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	Institutional Review Board

Abbreviation	Definition
ITT	intent-to-treat
LH	luteinizing hormone
LSIL	low-grade squamous intraepithelial lesion
NETA	norethindrone acetate
PI	Pearl Index
QD	once daily
QTcF	QTc corrected using Fridericia's formula
rITT	restricted intent-to-treat
STD	sexually transmitted disease
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
US	United States
VTE	venous thromboembolic event

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