# CLINICAL STUDY PROTOCOL

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| **Study Title:** | SPIRIT 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain |
| **Investigational Product:** | Relugolix |
| **Protocol Number:** | MVT-601-3102 |
| **Indication:** | Treatment of Endometriosis-Associated Pain |
| **Sponsor:** | Myovant Sciences GmbH<br>Viaduktstrasse 8 4051 Basel<br>Switzerland |
| **Regulatory Identifiers:** | IND# 076642<br>EudraCT # 2017-001632-19 |
| **Version and Effective Date:** | Original: 12-JUN-2017<br><br>Amendment 1: 12-MAR-2018 |

## CONFIDENTIALITY STATEMENT

# SPONSOR SIGNATURE PAGE

SPIRIT 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain

Protocol Number: MVT-601-3102

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

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# 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.

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| Principal Investigator Name (Printed) | Signature |
| Date | Site |

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# LIST OF ABBREVIATIONS

| Term | Explanation |
|---|---|
| Ab | antibody |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{0-24}$ | area under the concentration-time curve from time 0 to 24 hours |
| BP | blood pressure |
| CDF | cumulative distribution function |
| CFR | Code of Federal Regulations |
| $C_{max}$ | maximum plasma concentration |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYP | cytochrome P450 |
| DHEA | dihyroepiandrosterone |
| DNA | deoxyribonucleic acid |
| DXA | dual-energy x-ray absorptiometry |
| EAPS | Endometriosis-Associated Pain Severity |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| eDiary | electronic diary |
| EHP | Endometriosis Health Profile |
| EOT | End of Treatment |
| EQ-5D-5L | European Quality of Life Five-Dimension Five-Level Scale |
| FDA | (United States) Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GnRH | gonadotropin-releasing hormone |
| HBsAg | hepatitis B virus surface antigen |
| HCV | hepatitis C virus |
| HR | heart rate |
| ICH | International Conference on Harmonisation |
| ID | identification |
| IEC | Independent Ethics Committee |
| IgM | immunoglobulin M |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IVRS/IWRS | Interactive Voice/Web Recognition Service |
| LH | luteinizing hormone |

| Term | Explanation |
|---|---|
| LLN | lower limit of normal |
| MedDRA | Medical Dictionary for Regulatory Activities |
| miRNA | micro-ribonucleic acid |
| mITT | modified Intent-to-Treat |
| mmHg | millimeters of mercury |
| NMPP | nonmenstrual pelvic pain |
| NOAEL | no-observed-adverse-effect level |
| NOEL | no-observed-effect level |
| NRS | Numerical Rating Scale |
| NSAID | non-steroidal anti-inflammatory drug |
| Pap | Papanicolaou |
| PBAC | Pictorial Blood Loss Assessment Chart |
| PDF | probability density function |
| PGA | Patient Global Assessment |
| PGIC | Patient Global Impression of Change |
| PLD | phospholipidosis |
| QTc | corrected QT (interval) |
| QTcF | QT interval by the Fridericia correction |
| RNA | ribonucleic acid |
| ROC | receiver operating characteristics |
| RR | respiration rate |
| sB&B | Subject Modified Biberoglu and Behrman |
| ULN | upper limit of normal |
| US | United States |
| USP/NF | United States Pharmacopeia and the National Formulary |
| VAS | visual analogue score |
| WHO-DDE | World Health Organization Drug Dictionary Enhanced |

# 1. PROTOCOL SYNOPSIS

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| **Study Title** | SPIRIT 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Administered with and without Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain |
| **Protocol Number** | MVT-601-3102 |
| **Location** | Multinational, including North and South America, Europe, Australia, and New Zealand |
| **Study Centers** | Approximately 160 sites |
| **Study Phase** | Phase 3 |
| **Target Population** | Women aged 18 to 50 years diagnosed with endometriosis-associated pain |
| **Number of Patients Planned** | Approximately 600 (~400 relugolix and ~200 placebo) |

**Study Design**

The SPIRIT 2 study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate oral relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol (1.0 mg) and norethindrone acetate (0.5 mg) compared with placebo. Approximately 600 women with endometriosis-associated pain will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A, N ≈ 200), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B, N ≈ 200), or the placebo group (Group C, N ≈ 200). Stratification variables will include: geographic region (North America versus Rest of World) and years since surgical endometriosis diagnosis (< 5 or ≥ 5 years).

Eligible patients will have a diagnosis of endometriosis that has been visualized directly or during surgery and/or and/or documented by histopathology within 10 years of the Screening visit. Additionally, patients will have no history of chronic pelvic pain other than that caused by endometriosis and will not be using opioid analgesics or frequent non-opioid analgesics for chronic pain or recurring pain other than that due to endometriosis. Patients receiving hormonal contraceptives will discontinue these 28 to 56 days prior to the start of the single-blind Run-In Period. At the Screening visit, patients will answer questions as to the severity of their dysmenorrhea and nonmenstrual pelvic pain (NMPP). Only those whose pain is self-characterized as moderate, severe, or very severe for both dysmenorrhea and NMPP will proceed to additional Screening visit procedures and Run-In procedures. Patients who are not excluded by the results available at the end of the Screening visit will be dispensed an electronic diary (eDiary) and will begin a 35-day Run-In Period on the next day. During the single-blind Run-In Period, in which only patients will be blinded, the patients will take one placebo tablet and one placebo capsule each day and report their pain and analgesic medication use daily in the eDiary. Only study-specific analgesic medications should be used starting with the second Screening visit day (if the Screening visit is conducted over more than 1 day), during the Run-In Period, and subsequently. These medications will be taken for control of pain and not prophylactically. Final eligibility will be based on severity of pain determined by the specified Numerical Rating Scale (NRS) scores for dysmenorrhea and NMPP and Patient Global Impression of Change (PGIC) for NMPP obtained during the Run-In Period as defined in the inclusion and exclusion criteria. For patients with fewer than 3 dysmenorrhea scores during R1 through R35, Run-In will be continued through up to Day R70, with the Sponsor/designee approval (see Section 6.2, until 3 dysmenorrhea scores are obtained and these 3 scores will be used to determine eligibility for

dysmenorrhea. If needed, Run-In may also be extended for logistical reasons (eg, need for repeat endometrial biopsy) by an additional up to 35 days (ie, through Run-In Day R70) with Sponsor/designee approval.

Run-In Day R1 is defined as the day that the first dose of single-blind study drug was taken. Once eligibility has been confirmed, patients will be randomized on Baseline Day 1 and will begin double-blinded study drug treatment on the same day. The Run-In Period through the day prior to the first dose of randomized study drug will serve as the Baseline pain assessment period for the study. . During the Randomized Treatment Period, study participants will take the blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug will be taken on the day prior to the Week 24 visit.

Between the Baseline Day 1 and Week 24 visits, patients will attend visits every 4 weeks. During the Run-In Period and at the Week 12 and Week 24 visits, each patient will have an assessment of bone mineral density with dual-energy x-ray absorptiometry (DXA). Patients will complete a daily eDiary from the day prior to Run-In Day 1 through the Follow-Up visit to record study drug treatment, assessment of pain using the NRS, menstrual bleeding and its severity, analgesic use, and the functional effects of endometriosis-associated pain (using Subject Modified Biberoglu and Behrman [sB&B]). Evaluation of function (using Endometriosis Health Profile [EHP] - 30), quality of life questionnaires, PGICs, and Patient Global Assessments (PGAs) for pain and a PGA for function will be completed as specified in the Schedule of Activities. Patients will continue use of protocol-specified rescue analgesic medications, as needed, until the end of the Follow-Up Period.

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations including visual acuity, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and bone mineral density by DXA. Pharmacodynamics samples will be collected for assessment of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and progesterone at intervals during the study. Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug.

Patients who are not proceeding to the extension study and who have bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip relative to the baseline measurement at their Week 24/Early Termination visit or most recent scan will undergo further testing and follow-up to evaluate recovery (see Section 6.8 for details). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.8 for details). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8 for details).

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| **Study Objectives** | In women with endometriosis-associated pain, the study objectives are as follows:<br><u>Primary Efficacy Objectives</u><br>• To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on dysmenorrhea;<br>• To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on NMPP. |

Secondary Efficacy Objectives

- To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the following:
  - Function measured by the EHP-30 Pain Domain;
  - Dysmenorrhea measured by the NRS;
  - NMPP measured by the NRS;
  - PGA for dysmenorrhea;
  - PGIC for dysmenorrhea;
  - PGA for NMPP;
  - PGIC for NMPP;
  - Dyspareunia measured by the NRS;
  - PGIC for dyspareunia;
  - Dyspareunia-related functional effects (sB&B);
  - PGA for pain;
  - PGA for function;
  - Endometriosis-associated quality of life (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains of the EHP-30);
  - Dysmenorrhea-related functional effects (sB&B);
  - NMPP-related functional effects (sB&B).
- To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo on the following:
  - Dysmenorrhea measured by the NRS;
  - NMPP measured by the NRS;
  - Function measured by the EHP-30 Pain Domain.

Safety Objectives

- To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate;
- To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B;
- To determine the change in bone mineral density after 24 weeks of treatment with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate;
- To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate.

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| | Pharmacodynamic Objective<br>• To evaluate the pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with low-dose estradiol and norethindrone acetate.<br>Exploratory Objectives<br>• To determine the benefit of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes related to endometriosis as follows:<br>o Endometriosis-associated quality of life (EHP-30 total score);<br>o Effects of endometriosis on work (EHP Work Domain);<br>o Quality of life as assessed by the European Quality of Life Five-Domain Five-Level (EQ-5D-5L) scale. |

**Inclusion/Exclusion Criteria**

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

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing date of the informed consent form;
3. By the patient's report, had 2 consecutive regular menstrual cycles (ie, 21 to 35 days in duration) immediately prior to randomization. For patients who have washed off hormonal contraceptives, the 2 regular cycles must start after the first (withdrawal) bleeding following discontinuation of contraceptives;
4. Has agreed to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
5. Has a diagnosis of endometriosis and has had, within 10 years prior to signing the informed consent form, surgical or direct visualization and/or histopathologic confirmation of endometriosis, for example, during a laparoscopy or laparotomy;
6. During the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and for NMPP in the prior month;
7. During the Run-In Period Days R1 through R35, has at least 24 days of completed eDiary scores;
8. During the Run-In Period Days R1 through R35, has a dysmenorrhea NRS score $\geq$ 4.0 on at least 2 days AND
    a. Mean NMPP NRS score $\geq$ 2.5, OR
    b. Mean NMPP NRS score $\geq$ 1.25 AND NMPP NRS score $\geq$ 5.0 on $\geq$ 4 days;

    For patients with fewer than 3 dysmenorrhea scores during Days R1 - R35, dysmenorrhea scores from Days R36 – 70 will be included in the eligibility determination until a total of 3 dysmenorrhea scores from the Run-In Period are available.
9. Has menstruated for at least 3 days during the Run-In Period;
10. Is not expected to undergo gynecological surgery or other surgical procedures for treatment of endometriosis (including ablation, shaving, or excision) during the study, including during the Follow-Up Period, and the patient does not desire such treatment during this time frame;
11. Has a negative urine pregnancy test at the Screening visit and on the Baseline Day 1 visit;

12. Agrees to use contraception during the study and for 30 days following the last dose of study drug. Specifically, agrees to use nonhormonal contraception as described in Section 4.7 consistently during the Screening Period, Run-In Period, and the Randomized Treatment Period and for 30 days following treatment discontinuation. However, the patient is not required to use the specified nonhormonal contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening Period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle. Periodic abstinence is not acceptable;

13. Has an adequate endometrial (aspiration) biopsy performed during the Screening visit or Run-In Period or one that was locally performed within 6 months prior to Screening with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer)

    Note 1: Patients for whom polyps are detected on the biopsy but are either not evident on ultrasound or < 2.0 cm by ultrasound are eligible;
    Note 2: endometrial biopsies that were performed or repeated during the Run-In Period and meet criteria are acceptable;

14. If ≥ 39 years of age at the time of the Screening visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 2 or equivalent; see Appendix 1) during the Run-In Period or within 6 months prior to the Run-In Period.

Exclusion Criteria

1. Has a history of chronic pelvic pain that is not caused by endometriosis (eg, vaginismus, chronic pelvic infection, symptomatic hydrosalpinx, symptomatic dermoid, symptomatic corpus lutea, persistent symptomatic ovarian cyst, suspected ovarian torsion, or pelvic floor disorders);
2. Has had 4 or more prior laparoscopic or open abdominal or pelvic, surgical procedures for endometriosis;
3. During the Run-In Period, reports NMPP is "much better" on the PGIC for NMPP;
4. Has a transvaginal ultrasound during the Screening or Run-In Period demonstrating pathology other than endometriosis that could be responsible for or contributing to the patient's chronic pelvic pain or a clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

    Note 1: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal ultrasound or endometrial biopsy (eg, suspected intrauterine masses, equivocal endometrial findings, etc);

    Note 2: Transvaginal ultrasounds that were repeated during the Run-In Period and met criteria are acceptable;
5. Has any chronic pain or frequently recurring pain condition, other than endometriosis, that is treated with opioids or requires analgesics for ≥ 7 days per month;

6. Has had a surgical procedure for treatment of endometriosis within the 3 months prior to the Screening visit;
7. Has a history of previous non-response of NMPP or dysmenorrhea to gonadotropin-releasing hormone (GnRH) agonists, GnRH antagonists, or depot medroxyprogesterone acetate based on patient's report or treating physician's assessment of chart documentation. Note: A partial response to these drugs is not exclusionary;
8. Has unexplained vaginal bleeding outside of the patient's regular menstrual period, defined as bleeding occurring > 4 days outside the patient's usual range of menses duration;
9. 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);
10. Has bone mineral density z-score < -2.0 at spine, total hip, or femoral neck during the Run-In Period;
11. Has a gastrointestinal disorder affecting absorption or gastrointestinal motility;
12. Has used, is using or is anticipated to use prohibited medications (see Section 5.11 for prohibited medications and the exclusionary periods for these);
13. Patients receiving selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, or tricyclic antidepressants that have been recently started or undergone recent dose changes. Patients who have been on stable doses for at least 3 months and are anticipated to remain on stable doses during the study (including the Run-In Period) may be enrolled;
14. Has a history of or currently has osteoporosis, or other 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 bone mineral density eligibility criteria for the study are allowed;
15. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
16. 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;
17. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;

h. History of porphyria;

18. Has jaundice or known current active liver disease from any cause including non-alcoholic fatty liver disease, hepatitis A (hepatitis A virus immunoglobulin M [IgM]), hepatitis B (hepatitis B virus surface antigen [HBsAg]), or hepatitis C (hepatitis C virus [HCV] antibody [Ab] positive, confirmed by HCV ribonucleic acid [RNA]);
19. On the most recently documented Papanicolaou test, has any of the following cervical pathology: high-grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, or atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high-risk human papilloma virus testing is negative or if deoxyribonucleic acid (DNA) testing for human papilloma virus 16 and 18 is negative;
20. Has any of the following clinical laboratory abnormalities during the Screening or Run-In Period:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 times ULN (or > 2.0 times ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Estimated glomerular filtration rate < 60 mL/min/$m^2$ using the Modification of Diet in Renal Disease method;
    c. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
    d. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);
21. Has clinically significant cardiovascular disease including:
    a. Prior history of myocardial infarction;
    b. History of angina or significant coronary artery disease (ie, ≥ 50% stenosis);
    c. History of congestive heart failure;
    d. History of clinically significant ventricular arrhythmias such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes, Mobitz II second degree or third degree heart block without a permanent pacemaker in place or untreated supraventricular tachycardia (heart rate ≥ 120 beats per minute);
    e. QT interval by the Fridericia correction formula (QTcF) of > 470 msec on the Screening visit or Baseline Day 1 ECG;
    f. Hypotension, as indicated by systolic blood pressure < 84 millimeters of mercury (mmHg) on 2 repeat measures at least 15 minutes apart, or treated ongoing symptomatic orthostatic hypotension with > 20 mmHg decrease in systolic blood pressure one minute or more after assuming an upright position;
    g. Uncontrolled hypertension, as indicated by systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg on 2 repeat measures at least 15 minutes apart during the Screening Period;
    h. Bradycardia as indicated by a heart rate of < 45 beats per minute on the Screening visit or Baseline Day 1 ECG unless judged by the investigator to be due to physical fitness;
22. Has been a participant in an investigational drug or device study within the 1 month prior to the Screening visit;
23. Has a history of clinically significant condition(s) including, but not limited to the following:
    a. Untreated thyroid dysfunction (patients with adequately treated hypothyroidism who are stable on medication are not excluded);
    b. History of malignancy within the past 5 years or ongoing malignancy other than

curatively treated non-melanoma skin cancer or surgically cured Stage 0 in situ melanoma;

c. Any current psychiatric disorder that would, in the opinion of the investigator or medical monitor, impair the ability of the patient to participate in the study or would impair interpretation of their data. Patients with major depression, post-traumatic stress disorder, bipolar disorder, schizophrenia or other psychotic disorders, based on Diagnostic and Statistical Manual of Mental Disorders-5 criteria who have been unstable or not well controlled, based on the investigator's or mental health professional's judgement or whose history or stability cannot be ascertained, or whose psychiatric drug regimen has changed during the 3 months prior to the Screening visit or is expected to change during the study should not be enrolled;

24. Is currently pregnant or lactating, or intends to become pregnant during the study period through 1 month after the last dose of study drug or intends to donate ova during the study period or within 2 months after the last dose of study drug;
25. Has a contraindication or history of sensitivity to any of the study treatments or components thereof, including protocol-specified analgesic medications; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
26. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use);
27. Has participated in a previous clinical study that included the use of relugolix;
28. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
29. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor.

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| **Dose and Route of Administration** | Test Product (Randomized Treatment Group A and Group B)<br>• Group A: Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate in a co-formulated tablet. The low-dose hormonal add-back therapy will be over-encapsulated.<br>• Group B: Relugolix 40 mg tablet co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color for 12 weeks, followed by relugolix 40 mg tablet co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The active low-dose hormonal add-back therapy will be over-encapsulated.<br>Reference Product (Placebo Run-In and Randomized Treatment Group C)<br>• Group C: Placebo relugolix tablet manufactured to match relugolix in size, shape, and color will be co-administered orally once daily with a placebo capsule designed to match the over-encapsulated active low-dose hormonal add-back therapy in size, shape, and color. |

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| **Duration of Treatment** | Study treatment will be self-administered during the Run-In Period and during the 24-week Randomized Treatment Period. For women who will not be enrolling in an open-label extension study, there will be a 30-day Follow-Up Period after the end of treatment (ie, after the patient's last dose of study drug).<br><br>Concomitant Medicinal Products Systematically Prescribed for All Study Patients to be Used as Needed for Endometriosis-Associated Pain<br><br>Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug (NSAID) and a second-line opioid or opioid/acetaminophen combination for endometriosis-related pain relief, and are to be used as needed for endometriosis-associated pain. The specific analgesic drugs offered may differ for different countries or regions. |
| **Criteria for Evaluation** | Inferential efficacy assessments will be made between the following groups and placebo after 24 weeks of study treatment:<br><br>• Relugolix Group A: 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate;<br><br>• Relugolix Group B: 12 weeks of oral relugolix 40 mg once daily monotherapy followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate.<br><br>Descriptive assessment of treatment effect will be made between each relugolix group and placebo for safety outcomes and between each of the 2 relugolix groups for both efficacy and safety.<br><br>The Run-In Period through the day prior to the first dose of randomized study drug will establish the patient's baseline pain and the Randomized Treatment Period will establish the patient's response. The Week 24/End of Treatment (EOT) pain assessment period will use the pain scores from the last 35 days prior to last dose of study drug during the Randomized Treatment Period.<br><br>Co-Primary Endpoints<br><br>• Proportion of responders at the Week 24/EOT pain assessment period, based on their dysmenorrhea NRS scores recorded in a daily eDiary, in the relugolix 40 mg group co-administered with low-dose hormonal add-back therapy for 24 weeks versus placebo;<br><br>• Proportion of responders at the Week 24/EOT pain assessment period, based on their NMPP NRS scores recorded in a daily eDiary, in the relugolix 40 mg group co-administered with low-dose hormonal add-back therapy for 24 weeks versus placebo.<br><br>Secondary Endpoints<br><br>The change at Week 24 from Baseline in EHP-30 Pain Domain comparing Group A and Group C is a key secondary endpoint to which Type 1 error protection will be extended. The Statistical Analysis Plan will specify to which additional secondary endpoints Type 1 error protection will be extended.<br><br>• Change from Baseline at Week 24 in the EHP-30 Pain Domain scores in the relugolix 40 mg group co-administered with low-dose hormonal add-back therapy for 24 weeks versus placebo;<br><br>The following secondary endpoints will be assessed comparing Group A with |

Group C:

- Change from Baseline to Week 24/EOT in the mean dysmenorrhea NRS score;
- Change from Baseline to Week 24/EOT in the mean NMPP NRS score;
- Change from Baseline to Week 24/EOT in the severity scores on the PGA for dysmenorrhea;
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 24/EOT;
- Change from Baseline to Week 24/EOT in the severity scores on the PGA for NMPP;
- Proportion of patients who are better or much better on the PGIC for NMPP at Week 24/EOT.
- Change from Baseline to Week 24/EOT in the mean dyspareunia NRS scores.
- Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 24/EOT;
- Change from Baseline to Week 24/EOT in the mean dyspareunia functional impairment on the sB&B scale;
- Change from Baseline to Week 24/EOT in severity scores on the PGA for pain;
- Proportion of responders at Week 24/EOT based on their EHP-30 Pain Domain score;
- Change from Baseline to Week 24/EOT in function impairment on the PGA for function;
- Change from Baseline to Week 24/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
- Change from Baseline to Week 24/EOT in the mean dysmenorrhea functional impairment on the sB&B scale;
- Change from Baseline to Week 24/EOT in the mean NMPP functional impairment on the sB&B scale.

The following secondary endpoints will be assessed comparing Group B with Group C:

- Proportion of responders at the Week 24/EOT pain assessment period, based on their dysmenorrhea NRS scores recorded in a daily eDiary;
- Proportion of responders at the Week 24/EOT pain assessment period, based on their NMPP NRS scores recorded in a daily eDiary.
- Change from Baseline at Week 24/EOT in the EHP-30 Pain Domain scores.
- Proportion of responders at Week 24/EOT based on their EHP-30 Pain Domain score.

Dyspareunia analyses will be performed only in patients who had vaginal sexual intercourse during both the Baseline pain-assessment period and Randomized Treatment Periods.

Safety Endpoints

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

Pharmacodynamic Endpoints

- Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone.

Exploratory Endpoints

- Change from Baseline to Week 24/EOT in the EHP-30 scale total score;
- Change from Baseline to Week 24/EOT in the EHP-30 Work Domain score;
- Change from Baseline to Week 24/EOT in the EQ-5D-5L scale score.

**Statistical Methods**

Efficacy

The efficacy analyses will be conducted using a modified Intent-to-Treat (mITT) population defined as all randomized patients who have had at least one dose of randomized study drug, unless otherwise specified in Statistical Analysis Plan. The randomization ratio will be 1:1:1 among the 3 treatment groups:

Group A: Relugolix plus low-dose hormonal add-back therapy (N ≈ 200);

Group B: Relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy (N ≈ 200);

Group C: Placebo (N ≈ 200).

Randomization will be conducted centrally and stratified by geographic region and years since the diagnosis of endometriosis by direct surgical or laparoscopic visualization as follows:

- Geographic Region: North America versus Rest of World;
- Years since endometriosis diagnosis: $< 5$ or $\geq 5$ years.

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

This study has two co-primary endpoints defined as:

- Proportion of responders at the Week 24/EOT pain assessment period based on their dysmenorrhea NRS scores recorded in a daily eDiary;
- Proportion of responders at the Week 24/EOT pain assessment period based on their NMPP NRS scores recorded in a daily eDiary.

A responder (defined for dysmenorrhea and NMPP separately) is defined as a patient whose reduction in pain exceeds the defined response threshold (see below) and who did not have an increase in the use of rescue analgesic medications during the Week 24/EOT pain assessment period (last 35 days prior to last dose of study drug) compared with the Baseline pain assessment period. Baseline pain assessment will be based on the average of the values observed during the Run-In Period up to the day prior to the

date of first dose of randomized study drug treatment.

The threshold of a clinically meaningful response will be determined for dysmenorrhea and NMPP separately utilizing the anchor-based cumulative distribution function/probability density function method considering the PGA for dysmenorrhea and NMPP, respectively, as the anchors.

The primary hypothesis tested for each co-primary endpoint in this study is that relugolix co-administered with low-dose estradiol and norethindrone acetate (Group A) is superior to placebo (Group C). A logistic regression model will be used to compare relugolix to placebo for each pain measure (dysmenorrhea or NMPP). The responder status (responder versus non-responder) will be the dependent variable, treatment will be the main effect, baseline d pain score (dysmenorrhea or NMPP) and stratification factors will be the covariates.

The type I error rate for the primary analysis of each pain measure is controlled at 2-sided 0.05 significance level. The trial is positive if and only if both co-primary endpoints are met, eg, the p-value for each hypothesis test is $< 0.05$.

The point estimate and 2-sided 95% confidence interval for the difference in the proportions of responders for each pain measure will be calculated between the relugolix group and placebo group. The comparison of relugolix group A versus placebo for dysmenorrhea and NMPP on the NRS score and comparisons of both relugolix groups versus placebo will be performed in a similar fashion for the secondary efficacy endpoints using appropriate statistical methods. A closed testing procedure will be used to control the overall type I error rate of 5% across primary and key secondary endpoint(s) testing. Details of this procedure will be provided in the Statistical Analysis Plan.

Sample Size Estimation

For the assessment of the superiority of relugolix versus placebo in the percentage of responders for each individual co-primary endpoint (dysmenorrhea and NMPP), a sample size of approximately 200 patients in the relugolix arm (Group A) versus 200 patients in the placebo arm (Group C) will provide at least 95% power at 2-sided significance level of 0.05 to detect an absolute treatment difference of 20% between Group A and Group C, assuming a dropout rate of 20%. This will provide an overall power of at least 90% for the study to detect an absolute treatment difference of 20% for both co-primary endpoints simultaneously.

The responder rate for Group C is assumed to be between 30 to 35%. With an additional 200 patients in relugolix Group B, the total sample size for the study will be approximately 600 patients.

Safety

Safety assessments will include treatment-emergent adverse events, vital signs, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density. Safety analyses will be based on all randomized patients who receive any amount of randomized study drug (Safety Population). Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, higher level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Descriptive statistics will be used rather than inferential statistics. Laboratory values also will be classified by toxicity grade based on the National Cancer Institute CTCAE. Laboratory shift tables of the Baseline results to each of the subsequent visits will be produced. Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Baseline, Week 12, and Week 24 visits and the absolute and percent change from Baseline will be summarized. To evaluate the effects of low-dose hormonal add-back on bone mineral density loss, a formal treatment comparison of Group A with Group B will be performed on the percent change at Week 12 from Baseline in the bone mineral

density lumbar spine (L1-L4) using the pooled data from two replicate studies (MVT-601-3101 and MVT-601-3102).

A chartered independent Data Monitoring Committee will monitor safety data, including bone density assessments, on an ongoing basis during this trial.

Pharmacodynamic Endpoints

Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone will be summarized.

## 1.1. Schedule of Activities

**Table 1-1 Schedule of Activities for Study MVT-601-3102**

| **STUDY PERIOD** | **WASHOUT** | |
|---|---|---|
| Visit Name | **Washout** | |
| Visit Day (s) | ~2 weeks following last dose of washout medication | ~Every 4 weeks following last dose of washout medication |
| Visit Window (Days) | -90 | |
| Informed Consent | X[e] | |
| Telephone Contact* | X | X |
| Adverse Event Collection[hh] | X | |

*The purpose of the telephone contact is to evaluate pain control, to manage pain, if needed, and to reinforce the need for compliance with washout. If during these contacts, it is determined that a clinic visit is needed, then an unscheduled visit should be scheduled. Patients may require an adjustment to their analgesics during this period. There are no protocol restrictions for analgesic use during Washout through the first Screening Visit day.

[e]See footnote "e" below next table

[hh]See footnote "hh" below next table

| STUDY PERIOD | SCREEN-ING | RUN-IN | RANDOMIZED TREATMENT (DOUBLE-BLIND) | | | | | | | SAFETY FOLLOW-UP | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Run-In (Single-Blind)** | **Baseline Day 1** (Menstrual cycle Day 1-14) | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24/Early Termin-ation** | **Un-scheduled[a]** | **Follow-Up[b]** (~30 days after last study drug dose) |
| **Visit Day (s)** | **S1** | **R1 to R35** | **1[d]** | **29** | **57** | **85** | **113** | **141** | **169** | **-** | **199** |
| **Visit Window (days)** | **-15** | **+ 35** R70)[c] | **-** | **± 7** | **± 7** | **± 7** | **± 7** | ± 7 | -10/+20 | - | -3 to +10 |
| Informed Consent | X[e] | | | | | | | | | | |
| Endometriosis-Associated Pain Severity (EAPS) (Screening) | X[f] | | | | | | | | | | |
| Medical History | X | | | | | | | | | | |
| Review Inclusion and Exclusion Criteria | X | X | X | | | | | | | | |
| Prior/Concomitant Medications[g] | X | X | X | X | X | X | X | X | X | X | X |
| Vital Signs (BP, HR, RR, Temperature) | X | | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | |
| Weight | X | | X | | | | | | X | X | X |
| Complete Physical Exam | X | | X | | | | | | X | | |
| Visual Acuity | X[h, i] | | | | | | | | X[i] | X[a, i] | |
| Gynecologic Exam with Pap Test[j] | X[h] | | | | | | | | | X[a] | |
| Signs and Symptoms-Directed Physical Exam | | | | X | X | X | X | X | | X[a] | X |
| 12-Lead ECG | X | | X[k] | | | X | | | X | X[a] | X |

| STUDY PERIOD | SCREEN-ING | RUN-IN | RANDOMIZED TREATMENT (DOUBLE-BLIND) | | | | | | | SAFETY FOLLOW-UP | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Run-In (Single-Blind)** | **Baseline Day 1** (Menstrual cycle Day 1-14) | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24/Early Termin-ation** | **Un-scheduled[a]** | **Follow-Up[b]** (~30 days after last study drug dose) |
| **Visit Day (s)** | **S1** | **R1 to R35** | **1[d]** | **29** | **57** | **85** | **113** | **141** | **169** | **-** | **199** |
| **Visit Window (days)** | **-15** | **+ 35** R70)[c] | **-** | **± 7** | **± 7** | **± 7** | **± 7** | ± 7 | -10/+20 | - | -3 to +10 |
| Clinical Laboratory Tests[l] | X[l] | | X[l, k, m] | X | X | X | X | X | X[l, m] | X[a] | X |
| Genomics Sample[n] | | | X | | | X | | | X | X[a] | |
| Pharmacogenomics Sample[n] | | | X | | | | | | | X[a] | |
| Pharmacodynamics Sample[o] | | | X[k] | | | X | | | X | X[a] | X[o] |
| Urinalysis | X | | X[k] | | | | | | X | X[a] | |
| Pregnancy Test (Urine) | X | | X[p] | X | X | X | X | X | X | X[a] | X |
| Mammogram[q] | X | Or X | | | | | | | | | |
| Transvaginal Ultrasound[r] | X | | | | | | | | | | |
| Bone Densitometry[s] | X | Or X | | | | X | | | X[t, u] | X[a] | |
| Endometrial Biopsy[v] | X[h] | Or X | | | | | | | | | |
| Randomization | | | X | | | | | | | | |
| Dispense Study Drug per IVRS/IXRS kit assignments | X | | X | X | X | X | X | X | | X[a] | |
| Dispense or Prescribe Protocol-specified Analgesics Drugs[w] | X | | X | X | X | X | X | X | X | X[a] | |
| Treatment Compliance and Drug Accountability[x] | | | X | X | X | X | X | X | X | X[a] | X |

| STUDY PERIOD | SCREEN-ING | RUN-IN | RANDOMIZED TREATMENT (DOUBLE-BLIND) | | | | | | | SAFETY FOLLOW-UP | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Run-In (Single-Blind)** | **Baseline Day 1** (Menstrual cycle Day 1-14) | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24/Early Termin-ation** | **Un-scheduled[a]** | **Follow-Up[b]** (~30 days after last study drug dose) |
| **Visit Day (s)** | **S1** | **R1 to R35** | **1[d]** | **29** | **57** | **85** | **113** | **141** | **169** | **-** | **199** |
| **Visit Window (days)** | **-15** | **+ 35** R70)[c] | **-** | **± 7** | **± 7** | **± 7** | **± 7** | ± 7 | -10/+20 | - | -3 to +10 |
| Daily Self-Administration of Study Drug[y] | | X (Day R1 through day *prior* to Week 24/Early Termination visit) | | | | | | | | | |
| Take Study Drug in Clinic (rather than at home) | | | X | X | | X | | | | X[a] | |
| Take Protocol-specified Rescue Analgesics as Needed[z] | X | X | X | X | X | X | X | X | X | X | X |
| Daily eDiary[aa] | X[bb] | X | X | X | X | X | X | X | X | | X |
| Site Review of eDiary Data | | X | X | X | X | X | X | X | X | X[a] | X |
| Telephone Contact | | X[cc] | | | | | | | | | |
| EHP-30 Questionnaire[dd] | | | X[k] | | | X | | | X | X[a] | |
| Patient Global Assessment for Pain[dd] | X[ff] | | X[k] | X | X | X | X | X | X | X[a] | X |
| [on paper] Patient Global Assessment for dysmenorrhea and NMPP[ff] | X[gg] | | X[k] | X | X | X | X | X | X | X[a] | X |
| [on paper] Patient Global Assessment for Function[ee] | X[ff] | | X[k] | X | X | X | X | X | X | X[a] | X |
| Patient Global Impression of Change[dd] | | X[gg] | | | | X | | | X | X[a] | |
| EQ-5D-5L[dd] | | | X[k] | | | | | | X | X[a] | |
| [on paper] EHP Work Domain[ee] | | | X | | | | | | X | X[a] | |

| STUDY PERIOD | SCREEN-ING | RUN-IN | RANDOMIZED TREATMENT (DOUBLE-BLIND) | | | | | | | SAFETY FOLLOW-UP | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening** | **Run-In (Single-Blind)** | **Baseline Day 1** (Menstrual cycle Day 1-14) | **Week 4** | **Week 8** | **Week 12** | **Week 16** | **Week 20** | **Week 24/Early Termin-ation** | **Un-scheduled[a]** | **Follow-Up[b]** (~30 days after last study drug dose) |
| **Visit Day (s)** | **S1** | **R1 to R35** | **1[d]** | **29** | **57** | **85** | **113** | **141** | **169** | **-** | **199** |
| **Visit Window (days)** | **-15** | **+ 35** R70)[c] | **-** | **± 7** | **± 7** | **± 7** | **± 7** | ± 7 | -10/+20 | - | -3 to +10 |
| Adverse Event Collection[hh] | X | X | X | X | X | X | X | X | X | X | X |
| Status of Menstruation Recovery | | | | | | | | | | X[a] | X[ii] |

Abbreviations: BP, blood pressure; ECG, electrocardiogram; EHP, Endometriosis Health Profile; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; HR, heart rate; Pap, Papanicolaou; RR, respiration rate

a. Unscheduled visits may be conducted at the investigator's discretion when needed. The procedures indicated in this Schedule of Activities will be performed at the Unscheduled visit based on the purpose of the visit (eg, follow-up for an adverse event or abnormal laboratory test). The reason for the visit will be captured in the source documents.
b. Follow-Up visit: For women who do not continue into the open-label extension study (MVT-601-3103), a Follow-Up visit to assess safety will be scheduled for approximately 30 days after study drug is discontinued by the patient (ie, ~Week 28 for patients who complete the study or ~30 days after an Early Termination visit).
c. If needed, for logistical reasons (eg, need for repeat endometrial biopsy) or due to an insufficient number of dysmenorrhea scores during Run-In Days R1-R35, the Run-In Period may be increased by an additional up to 35 days (ie, through Run-In Day R70) with Sponsor/designee approval. The e-Diary should continue to be completed during the entire Run-In Period and study drug should be continued. Patients continuing in Run–In beyond Day R42 may require additional study drug to be dispensed to avoid interruption of drug during the Run-In Period. Contact the Sponsor/designee as soon as possible if there is an issue that may preclude randomization within 8 days following Day R35.
d. Baseline/Day 1 should be scheduled to occur no later than the day after Day R42 and timed to occur during Days 1 through 14 of the menstrual cycle whenever possible. If a Sponsor-approved window extension has been granted (see footnote c), then Baseline Day 1 should be scheduled to occur no later than 1 day after the end of that window.
e. May be signed up to 90 days prior to Screening procedures to allow for washout of hormonal treatments and other prohibited drugs, as needed.
f. Patients are to record their historical worst pain severity on menstrual days from their most recent menstrual cycle and nonmenstrual days from the prior month in the eDiary. Only patients who qualify on both questions (pain is at least "moderate") may proceed to additional screening procedures (see Section 6.2 for details).
g. Record all prescription and non-prescription drug and supplements used during the 30 days prior to the Screening visit through the Safety Follow-Up Period.
h. Complete procedure during the Screening Period; however, if re-testing is needed, it may be completed during the Run-In Period.

i. See Section 6.10.2.5 for instructions on testing visual acuity. Patients who qualify to enter the Run-In Period and whose presenting (ie, with corrective lenses, if applicable) visual acuity score is 90 or lower at the Screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history. For patients whose presenting visual acuity score has declined at the Week 24/Early Termination visit or at an Unscheduled visit, please see Section 6.8 for follow-up requirements.

j. The Papanicolaou test must be conducted for women without a test result within 2 years prior to the Screening visit. Re-measurement should be performed for inadequate samples or potentially false positive-results. Please see the Laboratory Manual for guidance on obtaining and submitting the sample to the central laboratory for analysis.

k. Complete procedure prior to administration of the first dose of study drug. The following must also be completed prior to randomization: urine pregnancy and 12-lead ECG.

l. Clinical laboratory tests at each visit include clinical chemistries and a complete blood count.
Screening laboratory tests may be repeated during the Run-In Period once, if necessary, at the investigator's discretion. Additional re-testing requires the approval of the medical monitor.
    - At the Screening visit, additional tests include: thyroid-stimulating hormone.
    - At the Baseline Day 1 visit, additional tests include: lipid profile, prolactin, 25 (OH) Vitamin D, and hemoglobin A1c. An additional sample will be collected at this visit and stored for possible future testing for presence of hepatitis A, B, and C to assess etiology of liver test abnormalities.
    - At the Week 24/Early Termination visit additional tests include: lipid profile, thyroid stimulating hormone, prolactin, and hemoglobin A1c.

m. Baseline Day 1 samples and Week 24 samples should be obtained in a fasted state (at least 8 hours). Water is allowed during the fasting period.

n. Pharmacogenomics and genomics samples (unless precluded by local law or regulations): If possible, the pharmacogenomics sample should be collected from consented patients at the Baseline Day 1 visit, but it may be collected at any time during the study through Week 24 (inclusive). The genomics sample should be collected at each of the visits indicated.

o. Pharmacodynamic samples: Collect samples for analysis of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone concentrations at indicated visits.
On the pharmacodyamic sample collection visit days, collect the sample pre-dose for the dose due on that day and administer study treatment after the pharmacodynamics sample collections are complete. At the Week 24 visit, the sample should be drawn prior to the MVT-601-3103 first dose for patients continuing into the extension.

p. The pregnancy test must be done prior to randomization.

q. Patients ≥ 39 years of age at the time of the Screening visit must have a normal mammogram (Breast Imaging Reporting and Data System category 1 or 2 or equivalent; see Appendix 1) during the Run-In Period or within 6 months prior to the Run-In Period.

r. Transvaginal ultrasound must be performed to confirm the absence of any significant pathology that might be responsible for the pelvic pain (see Exclusion Criterion #4 for details). The ultrasound will be read locally.

s. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading. Randomization should not proceed until the Run-In Period scan result from the central review is available.

t. Procedure not required at the Early Termination visit in patients whose last dose of study drug was during Week 6 or earlier or within 4 weeks after completion of the Week 12 scan. The procedure may be done if it will aid in the evaluation of an ongoing adverse event.

u. Schedule DXA as early as possible within the Week 24 visit window. Patients not proceeding to the extension study who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit or most recent study scan relative to baseline (Run-In Period) will undergo another bone densitometry scan at 6 (± 1) months after the Week 24/Early Termination visit scan to evaluate recovery and will be contacted to question them about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the repeat bone densitometry. The repeat bone densitometry will be submitted for central reading. It is recommended that this procedure be completed during Screening, whenever possible, rather than waiting until the Run-In Period.

v. Obtain sample with an endometrial suction curette (eg, Pipelle®). See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis. It is strongly recommended that this procedure be completed during Screening, rather than waiting until the Run-In Period. Patients who have a documented and adequate endometrial biopsy from within 6 months prior to Screening are not required to have another biopsy.
w. Please see the Study Reference Manual for information on where and how to obtain protocol-specified analgesic medications by country. At the Week 24 visit, patients who will not be proceeding to the extension study will be re-dispensed or prescribed protocol-specified analgesic drugs, if needed, to ensure sufficient supply until the Follow-Up visit. For patients proceeding to the extension study, refer to the protocol for study MVT-601-3103.
x. The patient should be asked to bring all study drug and study-specified analgesic medications to the clinic at each visit. All unused study drug should be collected from the patient at Baseline Day 1 and at each scheduled visit. For patients who will not proceed to the extension study, all study-specified analgesics should be collected from the patient at the Follow-Up visit. For patients who will proceed to the extension study, all study-specified analgesics should be collected from the patient at the Week 24 visit.
y. The patient will take single-blind study drug once daily during the Run-In Period. On the Baseline Day 1 visit, the patient will take the first dose of randomized, double-blind study drug in the clinic and then self-administer the randomized study drug once daily up to the Week 24/Early Termination visit. The last dose of study drug will be taken on the day ***prior*** to the Week 24/Early Termination visit. For patients continuing into the extension study, the first dose of study drug for the extension study will be given in the clinic during the Week 24 visit ***after*** blood tests and other Week 24 procedures have been completed and eligibility for the extension study is confirmed.
z. There are no protocol-restrictions for analgesic use during washout, through the first Screening Visit day. Starting with the second day of the Screening visit (or the first day of the Run-In Period, for patients whose Screening visit is only 1 day), and to the end of the study, patients should only take their study-specified analgesics for pain. Analgesics should **not** be taken prophylactically (ie, in anticipation of pain). See Section 5.7 for additional details.
aa. The eDiary data collection will include Numerical Rating Scale (NRS) pain scores, menstruation information (including severity of bleeding), analgesic drug use, date and time of study drug administration, and Subject Modified Biberoglu and Behrman (sB&B) scale scores.
bb. eDiary training should be performed when the eDiary is dispensed at the Screening visit. The eDiary should be dispensed one day prior to the start of the Run-In Period.
cc. Contact the patient within 4 to 7 days of the start of the Run-In Period (Days R4 to R7 inclusive) to reinforce the eDiary, rescue analgesic medication instructions, and study drug administration.
dd. Patient will enter her response(s) into a tablet device at the site. On visits when both tablet and paper questionnaires are being performed at the site, the patient should complete the tablet questionnaires *before* the paper questionnaires.
ee. Patient will enter her response onto a paper questionnaire at the site. Paper questionnaires should be done in the following order: PGA for dysmenorrhea, PGA for NMPP, PGA for function, and EHP Work Domain.
ff. The first Patient Global Assessment (PGA) evaluations will be done during the Screening visit.
gg. A Patient Global Impression of Change (PGIC) score for nonmenstrual pelvic pain (NMPP) will be completed on Day R35 (-2) within the eDiary.
hh. Collect serious adverse event information from the time of signed informed consent through the Follow-Up visit, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first. Collect nonserious adverse event information from the start of the Run-In Period (or from the time of signed informed consent if event was related to a study procedure) through the Follow-Up visit, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first. For patients entering the extension study, adverse event collection for this study will end at the Week 24 visit.
ii. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.

# 2. INTRODUCTION

## 2.1. Endometriosis-Associated Pain

Endometriosis is a common chronic condition occurring primarily in women of reproductive age. It is one of the most common gynecologic disorders, evident in 70 to 90% of women with pelvic pain symptoms [Practice Committee of the American Society for Reproductive Medicine, 2014]. The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% of women of reproductive age [Dunselman, 2014]. Symptoms range from minimal to severely debilitating.

The pathogenesis of endometriosis is the presence of endometrial glands and stroma to outside the uterine cavity. Although the ectopic endometriotic lesions are most commonly found in the pelvis, they may also be located in the bowel, in the pleural cavity, and elsewhere. Women with endometriosis have an increased risk of abdominopelvic pain, dysmenorrhea, and dyspareunia compared with controls without endometriosis [Practice Committee of the American Society for Reproductive Medicine, 2014]. In a study of 940 women with endometriosis, the most common symptom leading to diagnosis was dysmenorrhea in approximately 90%, pelvic pain in approximately 80%, and dyspareunia in approximately 45%, with 34% of women diagnosed on the basis of all three symptoms [Sinaii, 2008]. Presenting symptoms of infertility (25%) and endometrioma (ovarian mass) (20%) were also common [Sinaii, 2008].

The mechanisms of pain in endometriosis are generally postulated to involve production of substances such as growth factors and cytokines, the direct and indirect effects of active bleeding from endometriotic implants, and irritation of pelvic floor nerves or direct invasion of those nerves by infiltrating endometriotic implants [Practice Committee of the American Society for Reproductive Medicine, 2014].

According to the American Society for Reproductive Medicine Practice Committee, "Endometriosis is a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures" [Practice Committee of the American Society for Reproductive Medicine, 2014].

Although hysterectomy with bilateral salpingo-oopherectomy is a definitive treatment of endometriosis, the American Society of Reproductive Medicine recommends that this option be reserved as a last resort for women with debilitating endometriosis symptoms who have completed childbearing and have failed to respond to alternative treatments [Practice Committee of the American Society for Reproductive Medicine, 2014]. Other surgical options for treatment of endometriosis include uterosacral nerve ablation, presacral neurectomy, and laparoscopic resection. Rates of recurrent dysmenorrhea 1 and 3 years after laparoscopic surgery with uterosacral nerve ablation were not better than with laparoscopic surgery without nerve ablation in a large randomized trial. Presacral neurectomy, which involves interrupting the sympathetic innervation to the uterus, improves pain but is a technically challenging procedure associated with significant risk of bleeding from the adjacent venous plexus. Patients may also experience constipation and/or urinary retention postoperatively. Laparoscopic treatment of endometriosis was found to be more effective at reducing pain than diagnostic laparoscopy in a meta-analysis of 5 randomized controlled studies. While laparoscopic treatment is effective, pain can recur, and the option of performing multiple surgeries is limited by risks that include the development

of pelvic pain from adhesions and decreased ovarian reserve, resulting in reduced fertility. In one retrospective study, subsequent surgery was performed after laparoscopic treatment in 21%, 47%, and 45% of women after 2, 5, and 7 years, respectively [Practice Committee of the American Society for Reproductive Medicine, 2014].

Medical management of endometriosis includes analgesics and treatments aimed at decidualization followed by atrophy of endometrial tissue with reduction or antagonism of estrogen production and induction of amenorrhea. Compared to normal endometrium, endometriotic implants are characterized by overproduction of prostaglandins and local production of estrogens and cytokines, which synergize the activities of each other and promote implantation of ectopic endometrium. In addition, the implants have upregulated estrogen synthesis pathways [Practice Committee of the American Society for Reproductive Medicine, 2014]. Interventions that reduce ovarian estrogen production reduce this synergistic process, thereby reducing or eliminating endometriosis-associated pain.

Medical hormonal options include hormonal contraceptives, progestins, gonadotropin-releasing hormone (GnRH) agonists, danazol, and aromatase inhibitors. Because of lack of data supporting use of one treatment over another, the treatment choice is based upon symptom severity, patient preferences, side effects, efficacy, contraceptive needs, costs, and availability [Dunselman, 2014]. The main adverse effects of GnRH agonists relate to induction of a hypoestrogenic state (eg, bone mineral density loss and vasomotor symptoms) whereas danazol produces androgenic adverse effects such as hirsutism, weight gain, and deepening of the voice. Some patients treated with GnRH agonists also experience an initial “flare effect” (increased pain and bleeding), and this can result in premature discontinuation of treatment. Side effects of progestin treatment can include irregular uterine bleeding, weight gain, mood changes such as depression, and bone mineral density loss with long-term use of certain agents.

The goal of the relugolix phase 3 development plan is to demonstrate that relugolix can decrease dysmenorrhea and nonmenstrual pelvic pain (NMPP) in women with endometriosis safely through 12 months of therapy and to evaluate effects on pain-related quality of life and function. By enhancing the safety and tolerability of the active treatment arm with the co-administration of low-dose hormonal add-back therapy, the program ultimately aims to bring to women suffering endometriosis-associated pain a long-term oral medical therapy that significantly reduces pain and improves quality of life and provides an alternative to invasive procedures.

## 2.2. Relugolix

### 2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once daily oral medication for the treatment of endometriosis-associated pain. The proposed dose of relugolix is 40 mg administered orally once daily and the proposed doses of estradiol and norethindrone acetate are 1.0 mg and 0.5 mg once daily, respectively.

### 2.2.2. Pharmacology

Relugolix is an orally-active, potent, highly-selective high-affinity small molecule GnRH receptor antagonist with a novel structure.

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

### 2.2.3. Nonclinical Toxicology

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

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

plasma concentration [$C_{max}$] of 4.0 µg/mL), but did not prolong the QT interval in a human Thorough QT study at doses up to 360 mg ($C_{max}$ of 0.181 µg/mL).

### 2.2.4. Previous Human Experience

As of 10 January 2017, 1568[1] patients and healthy volunteers (1032 women and 536 men, including 643 female patients with endometriosis or uterine fibroids and 218 male patients with prostate cancer) had received at least 1 dose of relugolix in 21 completed (N = 13) or ongoing (N = 8) studies. Nine phase 1 studies in healthy volunteers and 4 phase 2 studies (including 1 in women with uterine fibroids and 2 in women with endometriosis) have been completed. Eleven clinical studies evaluating relugolix are ongoing as of 31 May 2017, including 5 phase 1 studies, 1 phase 2 study in men with prostate cancer, and 3 multinational phase 3 studies (1 in men with advanced prostate cancer and 2 in women with uterine fibroids) and 2 phase 3 studies conducted in Japan in women with uterine fibroids.

Among relugolix-treated patients, 158 women received relugolix 40 mg once daily (the proposed phase 3 dose) for at least 28 days and at least 200 men received relugolix 80 mg or 120 mg once daily for at least 24 weeks and for as long as 48 weeks.

Eighty-eight women have been treated with relugolix 40 mg once daily for at least 24 weeks. In addition, single doses up to 360 mg have been given to 34 women.

#### 2.2.4.1. Clinical Pharmacology, Pharmacokinetics, and Metabolism

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

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

[1] This comprises 1390 patients and healthy volunteers who received at least 1 dose of relugolix and 178 patients estimated to have received at least 1 dose of relugolix based on randomization in ongoing blinded phase 3 studies evaluating relugolix in women with uterine fibroids.

A 6-week phase 1 study (MVT-601-1001) conducted in the US in healthy premenopausal women evaluated the safety, pharmacokinetics, and pharmacodynamics profile of oral relugolix 40 mg once daily and relugolix 40 mg once daily in combination with estradiol/norethindrone acetate (1.0 mg/0.5 mg once daily). Median pre-dose trough estradiol concentrations in the relugolix alone arm were < 10 pg/mL; with the addition of estradiol/norethindrone acetate, these were increased to 21 pg/mL, and median peak concentrations were 49 pg/mL (at Week 6 visit). This trough and peak concentration range is consistent with the estradiol range associated with reduced loss of bone mineral density [Barbieri, 1992; Riggs, 2012]. Relugolix pharmacokinetics were similar to historic data. The estrogenic metabolite of norethindrone, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetics samples collected. The adverse event profile was similar to prior phase 1 studies, with a marked reduction in hot flushes noted in the relugolix plus hormonal add-back therapy in comparison with the relugolix alone arm.

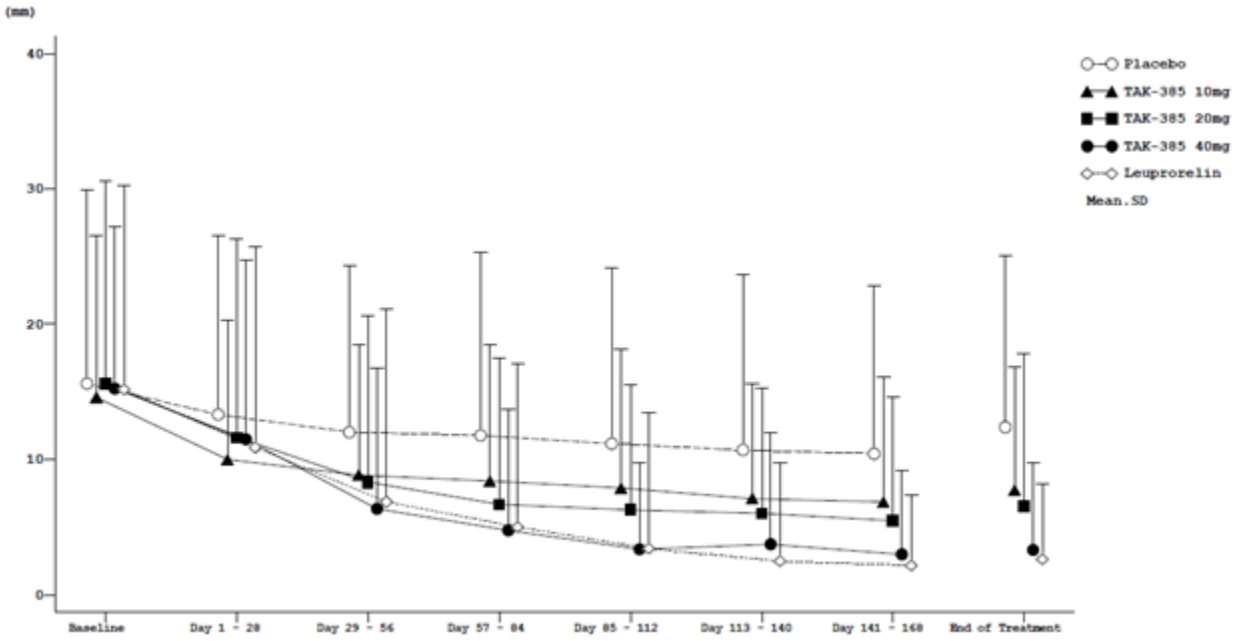
Relugolix is to be administered in the fasted state, as food decreases the extent of relugolix absorption (AUC) by approximately 19%. The exposure of relugolix is increased by inhibitors of P-glycoprotein up to 6-fold, but relugolix does not significantly impact the exposure of cytochrome P450 (CYP) 1A2, 2C9, 2D6, or 3A4 substrates. In a dedicated study, relugolix did not prolong the QTc interval.

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

**Endometriosis**

In a phase 2 study of women with endometriosis (TAK-385/CCT-101), 487 women were randomized to relugolix doses of 10, 20, or 40 mg or placebo, administered orally once daily over a 12-week period, or to leuprolide acetate (every 4-week injection) administered for 12 weeks. The study demonstrated dose-dependent decreases in pelvic pain as assessed by a 100 mm visual analogue score (VAS). The pain scores for pelvic pain were well-balanced across the groups at baseline and the means ranged from 14.6 to 15.6 mm. The changes from baseline in the VAS score (mean ± standard deviation) were -10.418 ± 11.0171 mm in the relugolix 40 mg group vs. -3.753 ± 10.5018 mm in the placebo group ($p < 0.0001$). All doses were better than placebo, with the greatest benefit observed at the highest dose evaluated, 40 mg once daily. The decrease in mean VAS pain score for the leuprolide group (-10.460 ± 10.3013 mm) was similar to that of the relugolix 40 mg group. The effects of relugolix on pain were maintained following an additional 12 weeks of treatment in the extension study (total of 24 weeks) (Figure 2-1). Estradiol levels were suppressed for the duration of the study.

**Figure 2-1 Mean Visual Analogue Score for Pelvic Pain in Patients with Endometriosis during 24 Weeks of Treatment with Relugolix, Placebo, or Leuprolide (TAK-385/OCT-101)**




Data Source: TAK-385/OCT- 101 Clinical Study Report Section 15.1 Fig 2.1.3

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

**Uterine Fibroids**

A phase 2 study (TAK-385/CCT-001) evaluated the efficacy, safety, pharmacokinetics, and pharmacodynamics of relugolix 10, 20, and 40 mg once daily for 12 weeks in 216 Japanese women with uterine fibroids and heavy menstrual bleeding. Heavy menstrual bleeding was defined for enrollment into the study as a score on the Pictorial Blood Loss Assessment Chart (PBAC) of at least 120; uterine fibroids were confirmed by ultrasound, magnetic resonance imaging, computed tomography, or laparoscopy. For the primary endpoint (proportion of patients with a total PBAC score of < 10 from Week 6 to 12), statistically significant dose-dependent differences were observed in all relugolix treatment groups compared to placebo. The

proportion was higher in the relugolix 40 mg group (83.6%) compared with 0% in the placebo group ($p < 0.0001$). In the relugolix 20 mg group, 43.6% of women responded and in the 10 mg group 20.8% responded, demonstrating a dose-response relationship. Of the women in the relugolix 40 mg group, 72.7% achieved amenorrhea from Week 6 to Week 12. Similarly, improvement with increasing dose was also observed in the secondary endpoints including change in myoma and uterine volumes and blood concentration of hemoglobin.

In the phase 2 uterine fibroid study, the most common treatment-emergent adverse events (occurring > 10% in any treatment group and more than placebo) were hot flush, metrorrhagia, menorrhagia, headache, genital hemorrhage, menstruation irregular and nasopharyngitis. With the exception of the incidence of nasopharyngitis in all treatment groups, these common adverse events were thought to be caused by the pharmacological effect of relugolix. The adverse events associated with menstruation were primarily reported in the first 28 days. Most of the adverse events were mild or moderate, and no serious treatment-emergent adverse event considered related to study drug was observed. Adverse events resulted in study drug discontinuation in 2 patients (hemoglobin decreased in a placebo patient; and tinnitus, libido decreased, menopausal depression, and hyperhidrosis in 1 patient treated with relugolix 20 mg once daily). Bone mineral density decreases appeared to correlate with increasing doses of relugolix. Women treated with placebo for 12 weeks had a mild loss of bone mineral density (mean ± standard deviation) of -0.24 ± 2.218% compared with -0.75 ± 2.350%, -2.01 ± 2.334%, and -2.28 ± 2.194% in the relugolix 10, 20, and 40 mg once daily groups, respectively. One patient had a positive pregnancy test after receiving approximately 46 days of relugolix 10 mg once daily (a dose that does not fully suppress estradiol). Study drug was discontinued. An ultrasound determined that the patient was 7 weeks pregnant. The patient subsequently had an uneventful pregnancy and delivered a healthy infant at 39 weeks.

Two phase 3 studies evaluating relugolix in women with uterine fibroids are ongoing in Japan. One study is assessing the effect of relugolix in women with moderate to severe pain associated with uterine fibroids, and the other is evaluating women with heavy menstrual bleeding associated with uterine fibroids. Two phase 3 multinational studies (LIBERTY 1 and LIBERTY 2) are also ongoing evaluating relugolix in women with uterine fibroids and heavy menstrual bleeding.

**Prostate Cancer**

Two phase 2 clinical studies of relugolix (C27002 and C27003) in men with advanced prostate cancer requiring androgen deprivation therapy were initiated in North America in 2014. Results from interim analyses of these two ongoing phase 2 studies (C27002 and C27003) indicate that after a single loading dose of relugolix, 320 mg, dosing at 80 and 120 mg once daily rapidly reduce and effectively maintain testosterone levels to below the castration threshold for at least 25 weeks of treatment, comparable to levels achieved by leuprolide acetate 22.5 mg every 3 months and degarelix 80 mg monthly following a loading dose of 240 mg. Specifically, relugolix 120 mg once daily (N = 36) achieved testosterone suppression to less than 50 ng/dL at 48 weeks in 92% (77.5 to 98.2%) of patients compared with 95% (75.1 to 99.9%) of those treated with leuprolide (N = 20) in study C27002. In a separate study (C27003), relugolix 120 mg once daily (N = 65) achieved testosterone suppression to less than 50 ng/dL at 24 weeks in 95% (87.1 to 99.0%) of patients compared with 89% (75.2 to 97.1%) of those treated with degarelix (N = 38).

A multinational phase 3 study (HERO) is ongoing evaluating relugolix 120 mg orally once daily in men with advanced prostate cancer.

**Safety Summary**

Overall, relugolix has been well tolerated. The majority of adverse events have been mild, consistent with the known mechanism of action of GnRH receptor antagonists, and resolved without treatment. As of 10 January 2017, 57 serious adverse events had been reported for 44 patients in the global relugolix safety database. Forty-one of these 57 serious adverse events were reported in 30 (3.5%) of approximately 860 patients treated with relugolix. These events arose predominantly in patients with prostate cancer (28/41 [68.3%] serious adverse events). Fifteen serious adverse events were reported in either comparator-treated (N = 8 events, 7/287 [2.4%]) or placebo-treated (N = 7 events; 6/187 [3.2%]) patients.

Based on the observed incidence of events in the relugolix phase 2 studies (placebo-controlled women's health studies and open-label active comparator prostate cancer studies), adverse drug reactions in women's health indications include hot flush, headache, hyperhidrosis, and loss of bone mineral density and adverse drug reactions in the prostate cancer indication include hot flush, fatigue, arthralgia, nausea, increased weight, gynecomastia, and night sweats.

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

# 3. STUDY OBJECTIVES AND ENDPOINTS

In women with endometriosis-associated pain, the study objectives and corresponding endpoints are as follows:

| Objectives | Endpoints |
|---|---|
| **Co-Primary Efficacy** | |
| The co-primary efficacy objectives and endpoints below are based on comparisons between Group A and Group C: | |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on dysmenorrhea. | • Proportion of responders at the Week 24/End of Treatment (EOT) pain assessment period, based on their dysmenorrhea Numerical Rating Scale (NRS) scores recorded in a daily electronic diary (eDiary), in the relugolix 40 mg group co-administered with low-dose hormonal add-back therapy for 24 weeks versus placebo. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on NMPP. | • Proportion of responders at the Week 24/EOT pain assessment period, based on their NMPP NRS scores recorded in a daily eDiary, in the relugolix 40 mg group co-administered with low-dose hormonal add-back therapy for 24 weeks versus placebo. |

| Objectives | Endpoints |
|---|---|
| **Secondary Efficacy** | |
| The secondary efficacy objectives and endpoints below are based on comparisons between Group A and Group C: | |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on function measured by the Endometriosis Health Profile (EHP)-30 Pain Domain. | • Change from Baseline at Week 24 in the EHP-30 Pain Domain scores. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on dysmenorrhea measured by the NRS. | • Change from Baseline to Week 24/EOT in the mean dysmenorrhea NRS score. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on NMPP measured by the NRS. | • Change from Baseline to Week 24/EOT in the mean NMPP NRS score. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the Patient Global Assessment (PGA) for dysmenorrhea. | • Change from Baseline to Week 24/EOT in the severity scores on the PGA for dysmenorrhea |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the Patient Global Impression of Change (PGIC) for dysmenorrhea. | • Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 24/EOT. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the Patient Global Assessment (PGA) for NMPP | • Change from Baseline to Week 24/EOT in the severity scores on the PGA for NMPP. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the PGIC for NMPP. | • Proportion of patients who are better or much better on the PGIC for NMPP at Week 24/EOT. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on dyspareunia measured by the NRS. | • Change from Baseline to Week 24/EOT in the mean dyspareunia NRS scores. |

| Objectives | Endpoints |
|---|---|
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the PGIC for dyspareunia. | • Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 24/EOT. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on effects on dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]). | • Change from Baseline to Week 24/EOT in the mean dyspareunia functional impairment on the sB&B scale. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the Patient Global Assessment (PGA) for pain. | • Change from Baseline to Week 24/EOT in the severity scores on the PGA for pain. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on function measured by the Endometriosis Health Profile (EHP)-30 Pain Domain. | • Proportion of responders at Week 24/EOT based on EHP-30 Pain Domain scores; |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on the PGA for function. | • Change from Baseline to Week 24/EOT in the function impairment on the PGA for function. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on endometriosis-associated quality of life (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains of the EHP-30). | • Change from Baseline to Week 24/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image). |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on dysmenorrhea-related functional effects (sB&B). | • Change from Baseline to Week 24/EOT in the mean dysmenorrhea functional impairment on the sB&B scale. |
| • To determine the benefit of relugolix 40 mg once daily co-administered with 24 weeks of low-dose estradiol and norethindrone acetate compared with placebo on NMPP-related functional effects (sB&B). | • Change from Baseline to Week 24/EOT in the mean NMPP functional impairment on the sB&B scale. |

| Objectives | Endpoints |
|---|---|
| The secondary efficacy objectives and endpoints below are based on comparisons between Group B and Group C: | |
| • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo on dysmenorrhea measured by the NRS. | • Proportion of responders at the Week 24/EOT pain assessment period, based on their dysmenorrhea NRS scores recorded in a daily eDiary. |
| • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo on NMPP measured by the NRS. | • Proportion of responders at the Week 24/EOT pain assessment period, based on their NMPP NRS scores recorded in a daily eDiary. |
| • To determine the benefit of relugolix 40 mg once daily for 12 weeks followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate compared with placebo on function measured by the EHP-30 Pain Domain. | • Change from Baseline at Week 24/EOT in the EHP-30 Pain Domain scores.<br>• Proportion of responders at Week 24/EOT based on EHP-30 Pain Domain scores. |
| **Safety** | |
| • To determine the safety of 24 weeks of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate. | • Treatment-emergent adverse events, change in vital signs (including weight), clinical laboratory tests, and electrocardiograms (ECGs). |
| • To determine the percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B. | • Percent change from Baseline to Week 12 in bone mineral density at the lumbar spine (L1-L4) in Group A compared with Group B as assessed by dual-energy x-ray absorptiometry (DXA). |
| • To determine the change in bone mineral density after 24 weeks of treatment with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate. | • Percent change from Baseline to Week 24 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. |
| • To determine the incidence of vasomotor symptoms with relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate. | • Incidence of vasomotor symptoms. |
| **Pharmacodynamic** | |
| • To evaluate the pharmacodynamic effects of 24 weeks of relugolix 40 mg once daily when co-administered with low-dose estradiol and norethindrone acetate. | • Changes from Baseline to Week 24 in pre-dose concentrations of LH, FSH, estradiol, and progesterone. |

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| • To determine the benefit of relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol and norethindrone acetate on patient-reported quality of life outcomes related to endometriosis as follows: | |
| ○ Endometriosis-associated quality of life (EHP-30 total score). | • Change from Baseline to Week 24/EOT in the EHP-30 scale total score. |
| ○ Effects of endometriosis on work (EHP Work Domain). | • Change from Baseline to Week 24/EOT in the EHP Work Domain score. |
| ○ Quality of life as assessed by the European Quality of Life Five-Domain Five-Level (EQ-5D-5L) scale. | • Change from Baseline to Week 24/EOT in the EQ-5D-5L scale score. |

# 4. INVESTIGATIONAL PLAN

## 4.1. Overall Study Design

The SPIRIT 2 study is an international phase 3 randomized, double-blind, placebo-controlled efficacy and safety study to evaluate oral relugolix 40 mg once daily co-administered with either 12 or 24 weeks of low-dose estradiol (1.0 mg) and norethindrone acetate (0.5 mg) compared with placebo. Approximately 600 women with endometriosis-associated pain will be enrolled and randomized 1:1:1 to the relugolix plus low-dose hormonal add-back therapy group (Group A, N ≈ 200), the relugolix monotherapy followed by co-administration with low-dose hormonal add-back therapy group (Group B, N ≈ 200), or the placebo group (Group C, N ≈ 200). Stratification variables will include: geographic region (North America versus Rest of World) and years since surgical endometriosis diagnosis (< 5 or ≥ 5 years).

Eligible patients will have endometriosis that has been visualized directly or during surgery and/or documented by histopathology within 10 years of the Screening visit. Additionally, patients will have no history of chronic pelvic pain other than that caused by endometriosis and will not be using opioid analgesics or frequent non-opioid analgesics for chronic pain or recurring pain other than that due endometriosis. Patients receiving hormonal contraceptives will discontinue these 28 to 56 days prior to the start of the single-blind Run-In Period. At the Screening visit, patients will answer questions as to the severity of their dysmenorrhea and NMPP. Only those whose pain is self-characterized as moderate, severe, or very severe for both dysmenorrhea and NMPP will proceed to additional Screening visit procedures and Run-In procedures. Patients who are not excluded by the results available at the end of the Screening visit will be dispensed an eDiary and will begin a 35-day Run-In Period on the next day. During the single-blind Run-In Period, in which only patients will be blinded, the patients will take one placebo tablet and one placebo capsule each day and report their pain and analgesic medication use daily in the eDiary. Only study-specific analgesic medications should be used starting with

the second day of the Screening visit (if the Screening visit is conducted over more than one day), during the Run-In Period, and subsequently. These medications will be taken for control of pain and not prophylactically. Final eligibility will be based on severity of pain determined by the specified NRS scores for dysmenorrhea and NMPP and PGIC for NMPP obtained during the Run-In Period as defined in the inclusion and exclusion criteria. For patients with fewer than 3 dysmenorrhea scores during R1 through R35, Run-In will be continued through up to Day R70, with the Sponsor/designee approval (see Section 6.2, until the 3 dysmenorrhea scores are obtained and these 3 scores will be used to determine eligibility for dysmenorrhea. If needed, Run-In may also be extended for logistical reasons (eg, need for repeat endometrial biopsy) by an additional up to 35 days (ie, through Run-In Day R70) with Sponsor/designee approval.

Run-In Day R1 is defined as the day that the first dose of single-blind study drug is taken. Once eligibility has been confirmed, patients will be randomized on Baseline Day 1 and will begin double-blinded study drug treatment on the same day. The Run-In Period through the day prior to the first dose of randomized study drug will serve as the Baseline pain assessment period for the study. During the Randomized Treatment Period, study participants will take double-blinded study treatment (1 tablet and 1 capsule) orally once daily for 24 weeks. The last dose of study drug will be taken on the day prior to the Week 24 visit.

Between the Baseline Day 1 and Week 24 visits, patients will attend visits every 4 weeks. During the Run-In Period and at the Week 12 and Week 24 visits, each patient will have an assessment of bone mineral density with DXA. Patients will complete a daily eDiary from the day prior to Run-In Day 1 through the Follow-Up visit to record study drug treatment, assessment of pain using the NRS, menstrual bleeding and its severity, analgesic use, and the functional effects of endometriosis-associated pain (sB&B). Evaluation of function (EHP-30), quality of life questionnaires, PGICs, and PGAs for pain will be completed during the visits in an electronic tablet and a PGA for function will be completed as specified in the Schedule of Activities. Patients will continue use of protocol-specified rescue analgesic medications, as needed, until the end of the Follow-Up Period.

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations including visual acuity, clinical laboratory tests, 12-lead ECGs, and bone mineral density by DXA. Pharmacodynamics samples will be collected for assessment of LH, FSH, estradiol, and progesterone at intervals during the study. Eligible patients, including women randomized to placebo, will be offered the opportunity to enroll in a 28-week open-label extension study where patients will receive relugolix co-administered with low-dose estradiol and norethindrone acetate. Patients who do not enroll into the extension study will have a Follow-Up visit approximately 30 days after the patient's last dose of study drug.

Patients who are not proceeding to the extension study and who have bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip relative to the Baseline measurement at their Week 24/Early Termination visit or most recent study scan will undergo further testing and follow-up to evaluate recovery (see Section 6.8 for details). Patients whose menses has not resumed as of the Follow-Up visit for unexplained reasons (eg, not explained by concomitant medications or medical procedures) will be contacted by telephone to determine if menses has resumed (see Section 6.8 for details). Patients with reductions in visual acuity will be referred for ophthalmology consultation (see Section 6.8 for details).

**Figure 4-1 MVT-601-3102 Study Schematic**

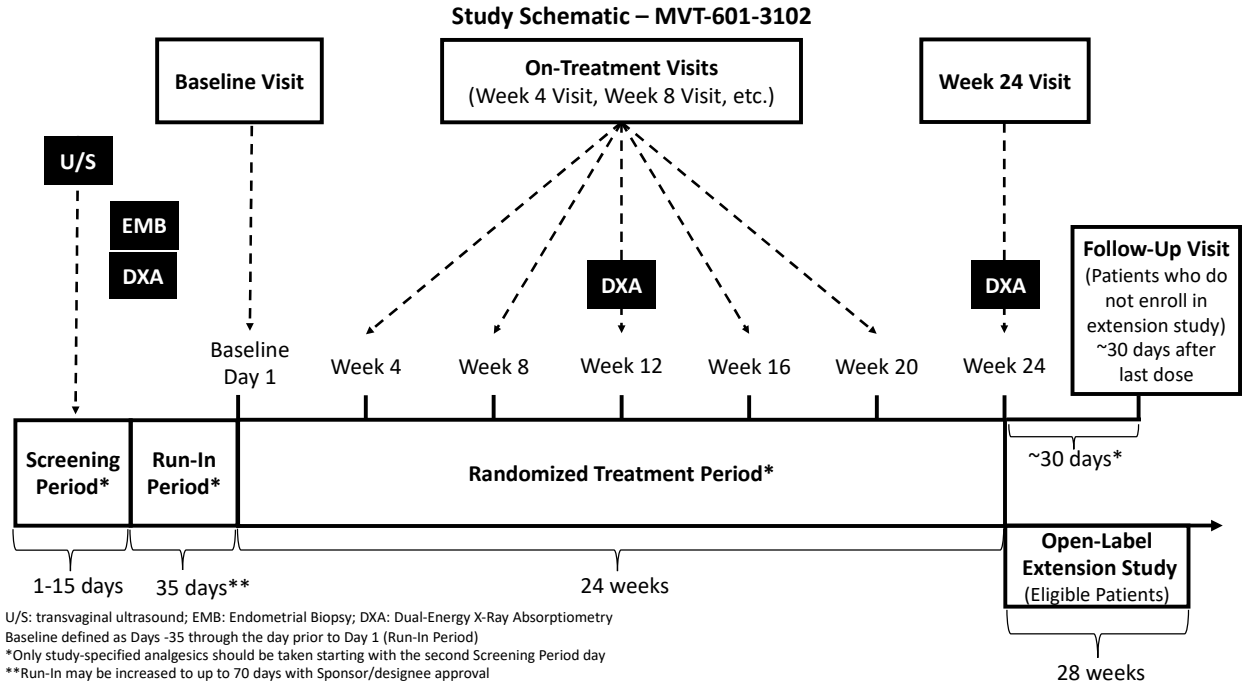
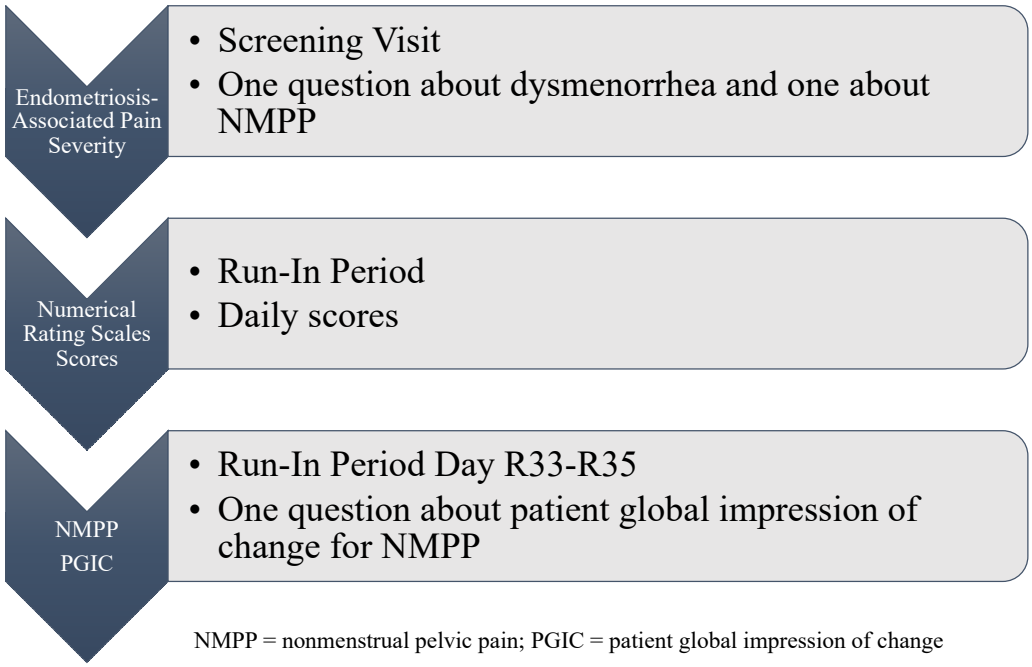



**Figure 4-2 Schematic of MVT-601-3102 Screening and Run-In Procedures for Determining Eligibility Based on Pain Scores**




NMPP = nonmenstrual pelvic pain; PGIC = patient global impression of change

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

This phase 3 study is one of two replicate studies designed to establish the efficacy and safety of relugolix 40 mg once daily in women with endometriosis-associated pain. This study will focus on the primary objective of demonstrating a reduction in dysmenorrhea and NMPP, the two most common symptoms that lead to diagnosis of endometriosis. The study is designed to demonstrate the benefit and safety of relugolix 40 mg once daily co-administered with low-dose estradiol (1.0 mg) and norethindrone acetate (0.5 mg) for 24 weeks. An additional relugolix arm dosed with 12 weeks of relugolix monotherapy 40 mg once daily followed by 12 weeks of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate will be used to provide an assessment of the requirement for the low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. An open-label extension study (MVT-601-3103) is planned to provide additional safety and efficacy data through a total of up to 52 weeks.

This study is randomized, double-blind, and placebo-controlled. Patients who meet the threshold levels of NRS worst pain scores for dysmenorrhea and NMPP during a single-blind placebo Run-In Period will receive double-blind treatment for 24 weeks. The purpose of the single-blind Run-In Period is to decrease from the randomized study population who exhibit a robust placebo response or sufficient placebo response that they do not meet the minimum threshold for pain severity. Rescue analgesic medications are specified by the protocol and no other analgesics will be allowed. Starting with the second day of the Screening visit, patients will take study-specified rescue analgesic medications as needed (but not prophylactically). Patients will report their pain scores and analgesic medication usage daily in an eDiary on instruments that have undergone validation and cognitive debriefing in women with endometriosis. Appropriately selected secondary endpoints aimed at evaluation of functional effects of endometriosis, dyspareunia, and quality of life related to endometriosis-associated pain are designed to further describe the clinical benefit of treatment.

The studies have two co-primary endpoints that separately evaluate the proportion of responders for dysmenorrhea and NMPP. The requirement to show efficacy on each endpoint is a more stringent requirement than a single primary endpoint because both of these important aspects of endometriosis-associated pain will need to be significantly improved by the treatment for the study to have met its primary objective. The level of pain severity reduction that constitutes a responder will be based on a clinically significant reduction determined by the patient-reported global assessments within the study. Use of analgesics is incorporated within the response definition.

Patients will visit the study site approximately every 4 weeks for safety evaluations, which include bone mineral density measurements, centrally-read ECGs, clinical laboratory assessments that include lipid measurements, visual acuity testing, physical examination, and vital signs. The study eligibility criteria have been designed to minimize risk to patients and rules for evaluation of liver test abnormalities, consistent with US Food and Drug Administration (FDA) guidance, have been incorporated into the protocol. A 28-week open-label extension study will be offered to all eligible women completing the 24-week phase 3 studies; this will provide a total of up to 52 weeks of safety and efficacy data in the women originally randomized to active therapy.

The study has three groups:

- Group A: relugolix 40 mg orally once daily co-administered with over-encapsulated estradiol (1.0 mg) and norethindrone acetate (0.5 mg) once daily, referred to as estradiol/norethindrone acetate for 24 weeks;
- Group B: relugolix 40 mg orally once daily for 12 weeks, followed by relugolix 40 mg orally once daily for another 12 weeks co-administered with estradiol/norethindrone acetate; and
- Group C: relugolix placebo tablet and an estradiol/norethindrone acetate placebo capsule once daily for 24 weeks.

The dose of relugolix was selected for the study (40 mg once daily) to maximally suppress estradiol levels in women with endometriosis-associated pain so that all women start from a stable floor of very low estrogen. Estradiol/norethindrone acetate will be co-administered to add-back, in a controlled fashion, a dose of estradiol known to prevent bone mineral density loss in the majority of women and to mitigate other tolerability adverse effects such as vasomotor symptoms. To ensure blinding, an over-encapsulated fixed-dose combination tablet of estradiol/norethindrone acetate will be co-administered with relugolix once daily.

Treatment Group A has been selected to provide the maximal benefit/risk ratio to women by providing relugolix 40 mg once daily, the dose known to maximally suppress estradiol levels and to provide the greatest decrease in endometriosis-associated pain, co-administered with low-dose estradiol/norethindrone acetate add-back therapy, to protect against bone mineral density loss and improve tolerability. Treatment Group B is intended to assess the requirement for low-dose hormonal add-back therapy to mitigate the adverse effects of relugolix monotherapy on bone mineral density loss and vasomotor symptoms. Placebo has been selected as the comparator because it facilitates double-blinding and allows for a clearer characterization of the safety and efficacy profile of relugolix, a new chemical entity, than would be possible with an active comparator. Furthermore, there is no single standard-of-care treatment for endometriosis-associated pain.

The selection of the proposed active treatment arm is supported by the following evidence-based reasons:

- Relugolix 40 mg once daily suppressed serum estradiol to less than postmenopausal levels, and significantly reduced endometriosis-associated pain in a well-designed large dose-finding phase 2 study.
- Low-dose hormonal add-back therapy has been demonstrated in combination with GnRH agonists and antagonists to attenuate loss in bone mineral density and the frequency of vasomotor symptoms such as hot flushes resulting from a hypoestrogenic state. This low-dose estradiol/norethindrone acetate therapy is currently approved for use in postmenopausal women to prevent osteoporosis and moderate to severe vasomotor symptoms.
- Because the bone is exquisitely sensitive to estrogen, particularly as compared with the doses of estrogen required to reverse the effects of relugolix on endometriosis-associated pain, the low doses of estradiol/norethindrone acetate that protect against bone mineral density loss are not expected to significantly impact the ability of relugolix to reduce endometriosis-associated pain.

## 4.3. Selection of Study Population

The study population will include approximately 600 premenopausal women aged 18 to 50 years with endometriosis-associated pain.

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

### 4.3.1. Inclusion/Exclusion Criteria

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

1. Has voluntarily signed and dated the informed consent form prior to initiation of any screening or study-specific procedures;
2. Is a premenopausal female aged 18 to 50 years old (inclusive) on the day of signing date of the informed consent form;
3. By the patient's report, had 2 consecutive regular menstrual cycles (ie, 21 to 35 days in duration) immediately prior to randomization. For patients who have washed off hormonal contraceptives, the 2 regular cycles must be after the first (withdrawal) bleeding following discontinuation of contraceptives;
4. Has agreed to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
5. Has a diagnosis of endometriosis and has had, within 10 years prior to signing the informed consent form, surgical or direct visualization and/or histopathologic confirmation of endometriosis, for example, during a laparoscopy or laparotomy;
6. During the Screening visit, the patient reports moderate, severe, or very severe pain during the most recent menses and for NMPP in the prior month;
7. During the Run-In Period Days R1 through R35, has at least 24 days of completed eDiary scores;
8. During the Run-In Period Days R1 through R35, has a dysmenorrhea NRS score $\geq$ 4.0 on at least 2 days AND
    a. Mean NMPP NRS score $\geq$ 2.5, OR
    b. Mean NMPP NRS score $\geq$ 1.25 AND NMPP NRS score $\geq$ 5.0 on $\geq$ 4 days;

    For patients with fewer than 3 dysmenorrhea scores during Days R1 - R35, dysmenorrhea scores from Days R36 – 70 will be included in the eligibility determination until a total of 3 dysmenorrhea scores from the Run-In Period are available.
9. Has menstruated for at least 3 days during the Run-In Period;
10. Is not expected to undergo gynecological surgery or other surgical procedures for treatment of endometriosis (including ablation, shaving, or excision) during the study, including during the Follow-Up Period, and the patient does not desire such treatment during this time frame;

11. Has a negative urine pregnancy test at the Screening visit and on the Baseline Day 1 visit;
12. Agrees to use contraception during the study and for 30 days following the last dose of study drug. Specifically, agrees to use nonhormonal contraception as described in Section 4.7 consistently during the Screening Period, Run-In Period, and the Randomized Treatment Period and for 30 days following treatment discontinuation. However, the patient is not required to use the specified nonhormonal contraception if she:
    a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Screening Period;
    b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Screening visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram and no evidence of "post-Essure syndrome" in the investigator's opinion);
    c. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above; or
    d. Practices total abstinence from sexual intercourse as her preferred lifestyle. Periodic abstinence is not acceptable;
13. Has an adequate endometrial (aspiration) biopsy performed during the Screening visit or Run-In Period or one that was locally performed within 6 months prior to Screening with results showing no clinically significant endometrial pathology (hyperplasia, polyp, or endometrial cancer).
    Note 1: Patients for whom polyps are detected on the biopsy but are either not evident on ultrasound or < 2.0 cm by ultrasound are eligible.
    Note 2: endometrial biopsies that were performed or repeated during the Run-In Period and meet criteria are acceptable;
14. If ≥ 39 years of age at the time of the Screening visit, has a normal mammogram (Breast Imaging Reporting and Data System category 1 to 2 or equivalent; see Appendix 1) during the Run-In Period or within 6 months prior to the Run-In Period.

Exclusion Criteria

1. Has a history of chronic pelvic pain that is not caused by endometriosis (eg, vaginismus, chronic pelvic infection, symptomatic hydrosalpinx, symptomatic dermoid, symptomatic corpus lutea, persistent symptomatic ovarian cyst, suspected ovarian torsion, or pelvic floor disorders);
2. Has had 4 or more prior laparoscopic or open abdominal or pelvic, surgical procedures for endometriosis;
3. During the Run-In Period, reports NMPP is "much better" on the PGIC for NMPP;
4. Has a transvaginal ultrasound during the Screening or Run-In Period demonstrating pathology other than endometriosis that could be responsible for or contributing to the patient's chronic pelvic pain or a clinically significant gynecological disorder determined by the investigator to require further evaluation and/or treatment during the study;

    Note 1: Saline or gel contrast is not routinely required. Use of such contrast is required only when the endometrium cannot be evaluated or when there are ambiguous and potentially exclusionary findings on the transvaginal ultrasound or endometrial biopsy (eg, suspected intrauterine masses, equivocal endometrial findings, etc);

Note 2: Transvaginal ultrasounds that were repeated during the Run-In Period and met criteria are acceptable;

5. Has any chronic pain or frequently recurring pain condition, other than endometriosis, that is treated with opioids or requires analgesics for ≥ 7 days per month;
6. Has had a surgical procedure for treatment of endometriosis within the 3 months prior to the Screening visit;
7. Has a history of previous non-response of NMPP or dysmenorrhea to GnRH agonists, GnRH antagonists, or depot medroxyprogesterone acetate based on patient's report or treating physician's assessment of chart documentation. Note: A partial response to these drugs is not exclusionary;
8. Has unexplained vaginal bleeding outside of the patient's regular menstrual period, defined as bleeding occurring > 4 days outside the patient's usual range of menses duration;
9. 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);
10. Has bone mineral density z-score < -2.0 at spine, total hip, or femoral neck during the Run-In Period;
11. Has a gastrointestinal disorder affecting absorption or gastrointestinal motility;
12. Has used, is using or is anticipated to use prohibited medications (see Section 5.11 for prohibited medications and the exclusionary periods for these);
13. Patients receiving selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, or tricyclic antidepressants that have been recently started or undergone recent dose changes. Patients who have been on stable doses for at least 3 months and are anticipated to remain on stable doses during the study (including the Run-In Period) may be enrolled;
14. Has a history of or currently has osteoporosis, or other 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 bone mineral density eligibility criteria for the study are allowed;
15. Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than calcium and vitamin D preparations to treat bone mineral density loss;
16. 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;

17. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
    a. Known, suspected, or history of breast cancer;
    b. Known or suspected estrogen-dependent neoplasia;
    c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Baseline Day 1 visit;
    d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
    e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
    f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
    g. Migraine with aura;
    h. History of porphyria;
18. Has jaundice or known current active liver disease from any cause including non-alcoholic fatty liver disease, hepatitis A (hepatitis A virus immunoglobulin M [IgM]), hepatitis B (hepatitis B virus surface antigen [HBsAg]), or hepatitis C (hepatitis C virus [HCV] antibody [Ab] positive, confirmed by HCV ribonucleic acid [RNA]);
19. On the most recently documented Papanicolaou test, has any of the following cervical pathology: high-grade cervical neoplasia, atypical glandular cells, atypical endocervical cells, or atypical squamous cells favoring high grade. Of note, patients with atypical squamous cells of undetermined significance and low-grade cervical neoplasia may be included in the study if high-risk human papilloma virus testing is negative or if deoxyribonucleic acid (DNA) testing for human papilloma virus 16 and 18 is negative;
20. Has any of the following clinical laboratory abnormalities during the Screening or Run-In Period:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN), or bilirubin (total bilirubin) > 1.5 times ULN (or > 2.0 times ULN if secondary to Gilbert's syndrome or pattern consistent with Gilbert's syndrome);
    b. Estimated glomerular filtration rate < 60 mL/min/$m^2$ using the Modification of Diet in Renal Disease method;
    c. Hypocalcemia (< lower limit of normal [LLN]) or hypercalcemia (> ULN);
    d. Hypophosphatemia (< LLN) or hyperphosphatemia (> ULN);

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

25. Has a contraindication or history of sensitivity to any of the study treatments or components thereof, including protocol-specified analgesic medications; or has a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates study participation;
26. Has a prior (within 1 year of the Screening visit) or current history of drug or alcohol abuse disorder according to Diagnostic and Statistical Manual of Mental Disorders-5 (all patients must be questioned about their drug and alcohol use);
27. Has participated in a previous clinical study that included the use of relugolix;
28. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, or sibling);
29. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, including contraception requirements, as determined by the investigator, sub-investigator, or medical monitor.

## 4.4. Screening

A Patient identification (ID) number will be assigned by the using Interactive Voice/Web Recognition Service (IVRS/IWRS) to each patient who signs an informed consent form and begins the screening period. This number will also serve as the Patient ID number following randomization. A patient ID will be needed for Screening tests and eDiary and tablet device set up. Screening failures are patients who consent to participate in the clinical study but are never randomized. When patients are screen failed from the study, they must be deactivated from the study in the IVRS/IWRS and the eDiary and tablet device. Re-screening is described in Section 6.3.4

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

After the completion of the eDiary through Day R35, the site staff will confirm transmission of the eDiary data. The sponsor (or designee) will determine the pain score eligibility and approve the patient's enrollment in writing. Once the site has received approval, the patient may undergo her Baseline Day 1 visit. After confirming that all inclusion criteria and no exclusion criteria are met, the site will randomize the patient to treatment by using the IVRS/IWRS during the patient's Baseline Day 1 visit. The IVRS/IWRS will assign the patient a study treatment kit numbers available at the site according to the randomization code.

## 4.6. Removal of Patients from Therapy

Completion of the Week 24 visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from

randomized study treatment for any reason will undergo the assessments for the Early Termination visit (see Schedule of Activities, Section 1.1) and will have a Follow-Up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study drug). When patients complete the study or early terminate from the study, they must be deactivated from the study in the IVRS/IWRS, eDiary, and tablet device.

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

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after randomization that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QTcF prolongation of more than 500 msec as read by a cardiologist;
- Patients who are, in the opinion of the investigator or the medical monitor, grossly non-compliant with the protocol requirements. Gross noncompliance includes < 75% compliance with the study drug over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive months) with < 50% of the required number of days eDiary completion. Investigators will follow-up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;
- Patients whose treatment assignment has been unblinded by the investigative site will be permanently discontinued from treatment;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.6 for information on pregnancy reporting);
- Should a patient fail to attend the clinic for a required study visit within the protocol-defined window, the site should attempt to contact the patient and reschedule the missed visit as soon as possible. Rescheduled visits conducted outside the visit window for the scheduled visit will be considered unscheduled. The site should also counsel the patient on the importance of maintaining the assigned visit schedule and determine whether the patient can and/or should continue in the study based on previous non-compliance. In cases where the patient does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the patient. The site should attempt at least 3 documented telephone calls and if necessary a

certified letter to the patient's last known mailing address so that they can appropriately be withdrawn from the study with a primary reason of "Lost to follow-up."

## 4.7. Contraception/Pregnancy Avoidance

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

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

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

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

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

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

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

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

# 5. TREATMENTS

## 5.1. Treatments Administered

During the single-blind Run-In Period, all patients will receive a relugolix placebo tablet plus an estradiol/norethindrone acetate placebo capsule. Patients will be kept blinded to the treatment.

Following the Run-In Period, patients will be randomized to receive one of the following double-blinded oral study treatments:

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

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

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

**Table 5-1 Description of MVT-601-3102 Study Drugs during the Single-Blind Run-In Period**

| Name of Investigational Product | Relugolix Placebo | Estradiol/Norethindrone Acetate Placebo |
|---|---|---|
| **Formulation Description** | Round film-coated pink tablet | A Swedish orange capsule with placebo back-fill material |
| **Dosage Form** | Tablet | Capsule |
| **Unit Dose Strength** | 0 mg | 0 mg |
| **Route of Administration/ Duration** | Oral once daily | Oral once daily |

**Table 5-2 Description of MVT-601-3102 Study Drugs during the Double-Blind Randomized Treatment Period**

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

Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug (NSAID) and a second-line opioid or opioid/acetaminophen combination for endometriosis-related pain relief as required. The specific analgesic drugs offered may differ for different countries or regions. A list of study-specified analgesics is provided in Appendix 8. For directions on prescribing rescue analgesic medications, see Section 5.7.

## 5.2. Identity of Investigational Product

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

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

### 5.2.1. Product Characteristics

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

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

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

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

## 5.3. Randomization and Stratification

At the Baseline Day 1 visit, patients will be randomized in a 1:1:1 ratio to 1 of 3 treatment groups, as described in Table 5-3.

**Table 5-3 Protocol MVT-601-3102 Treatment Group Randomization**

| Treatment Group | Randomized Treatment | Approximate Number of Patients |
|---|---|---|
| Group A | Relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 24 weeks | 200 |
| Group B | Relugolix 40 mg tablet co-administered with estradiol/norethindrone acetate placebo capsule for 12 weeks followed by relugolix 40 mg tablet co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate capsule for 12 weeks | 200 |
| Group C | Relugolix placebo tablet co-administered with estradiol/norethindrone acetate placebo capsule for 24 weeks | 200 |

Randomization will be stratified by geographic region and duration of endometriosis as follows:

- Geographic region: North America versus Rest of World; and
- Years since surgical endometriosis diagnosis: $< 5$ or $\geq 5$ years.

Patients are assigned to 1 of the 3 treatment groups in accordance with the randomization schedule (see additional information on randomization in Section 4.5).

## 5.4. Directions for Administration

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

The study treatment should be taken in the fasted state (see Section 6.5 for details) in the morning, at least 1 hour before breakfast. If dosing is missed in the morning for any reason, the study treatment may be taken later in the day, under fasting conditions, at least 1 hour before or 2 hours after eating a meal. The study treatment should be taken as close as possible to the same time of morning each day.

On selected clinic visit days, study drug will be administered in the clinic (refer to Section 1.1 for the visits during which patients take study drug in the clinic rather than at home).

## 5.5. Dose Reduction/Dose Administration

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

## 5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location at room temperature. Follow storage conditions described on the drug labeling.

A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug is provided in the Study Reference Manual. The investigator is responsible for study drug accountability, reconciliation, and record maintenance, including receipt, reconciliation, and final disposition records and their secure storage.

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

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

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

Details on analgesic medications are provided in Appendix 8.

## 5.7. Rescue Analgesic Medications

Management of endometriosis-associated pain often requires treatment with analgesics and some patients require treatment with opioid drugs. Two tiers of pain medications are specified for this trial. Only study-specific Tier 1 and Tier 2 analgesic medications (see Appendix 8) should be taken starting with the second day of the Screening visit (if the Screening visit is conducted over more than one day), during the Run-In Period, and subsequently. Analgesic medications will be taken for control of pain and not prophylactically. There are no protocol-restrictions for analgesic use during washout, through the first Screening Visit day.

If a patient develops uncontrolled endometriosis-associated pain during the study despite use of the study-specified analgesics or an intolerance to a study-specified analgesic, please contact the medical monitor.

Short-term use of non-study specified analgesics for the treatment of an intercurrent event (eg, injury or surgery) is allowed, if required. Such events should be reported as adverse events.

Investigators must instruct the patient on the use of ibuprofen 200 mg tablets (ie, number of tablets per dose, dosing frequency, maximum number of tablets per day) . For patients who may need the Tier 2 analgesic medication, a prescription should also be written for this prior to the

start of the Run-In Period. This is to ensure that patients do not endure unnecessary pain during the conduct of the study.

Quantities of opioids prescribed should be based on the patient's expected usage until the next study visit. Prescriptions for Tier 1 and Tier 2 rescue analgesic medications should be in accordance with their full prescribing information (ie, the local product labeling) and prescriptions for opioids should not provide for any refills. Patients should be counseled on the safe use of opioids.

Patients who are not prescribed the Tier 2 medication at Screening, for example, because requirement for analgesics beyond the Tier 1 medication is not expected (eg, based on pain level and/or recent analgesic requirements) should be advised to contact the investigator if pain is inadequately controlled with the Tier 1 medication alone. To avoid experiencing extended periods of uncontrolled pain, patients who require the Tier 2 medication should get a prescription from the investigator and initiate treatment with the Tier 2 medication as soon as feasible.

Use of protocol-specified rescue analgesic medications and any other analgesics taken for any type of pain, must be recorded by the patient in the e-Diary during the Run-In Period, Treatment Period, and Follow-up Period of the study.

## 5.8. Blinding

During the single-blind Run-In Period, only patients will be blinded. During the double-blind Randomized Treatment and Follow-Up Period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study will be blinded to treatment assignment, with the exception of an unblinded statistician(s) who is responsible for developing the randomization codes and presenting unblinded data to the Data Monitoring Committee if requested. The blind will be maintained during assessment of pharmacodynamic testing.

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

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

## 5.9. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and should bring all unused and used study drug to each study visit. At the Baseline Day 1 visit, Week 12 and Week 24/ET visit, all used and unused study drug kits should be retained at the site. New study drug should be

dispensed as described in Section 1.1 (Schedule of Activities). At all other visits, only used study drug kits should be retained at the site. Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the randomized study drug treatment, it may be appropriate to withdraw the patient from the study (see Section 4.6 for details). Because of the importance to both safety and efficacy evaluation, patients who are non-compliant with eDiary completion or study drug use must undergo an Unscheduled visit to evaluate reasons for non-compliance and to develop a plan to improve compliance. Failure to improve compliance may result in the sponsor withdrawing the patient from further study treatment (including study analgesics) and/or discontinuation from the study (see Section 4.6 for details).

All patients should be reinstructed about the dosing requirement and eDiary compliance during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

## 5.10. Treatment after the End of Study

Patients who complete 24 weeks of treatment on this study and wish to continue therapy may be eligible to continue treatment in the extension study MVT-601-3103. Eligibility criteria are set forth in that protocol. For patients continuing into the extension study, the first dose of study drug for the extension study will be given in the clinic during the Week 24 visit ***after*** blood tests and other Week 24 procedures have been completed and eligibility for the extension study is confirmed.

## 5.11. Prior and Concomitant Medications and Non-Drug Therapies

### 5.11.1. Prohibited Medications

Table 5-4 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

**Table 5-4 Prohibited Hormonal Medications and Windows of Exclusion**

| Drug Class | Examples | Window of Exclusion | |
|---|---|---|---|
| | | Prior to the Run-In Period | During the Study |
| Estrogens | estradiol valerate<br>conjugated estrogens<br>Ethinyl estradiol | 56 days<br>(16 weeks for depot subcutaneous or intramuscular injections) | Not allowed (other than the study drugs) |
| Hormonal contraceptives, contraceptive patches, and vaginal rings | combined or progestin only, Nuva Ring | 28 days | Not allowed |
| Selective estrogen receptor modulators | raloxifene<br>bazedoxifene<br>lasofoxifene<br>clomifene<br>tamoxifen | 56 days | Not allowed |
| Selective progesterone receptor modulators | mifepristone<br>ulipristal acetate | 6 months | Not allowed |
| Progestins and progestin implants | dienogest<br>drospirenone<br>norethindrone<br>medroxyprogesterone<br>cyproterone<br>etonogestrel | 56 days<br>(12 weeks for depot subcutaneous or intramuscular injections) | Not allowed (other than the study drugs) |
| GnRH analogues | leuprolide acetate injection, also known as leuprorelin<br>goserelin acetate injection<br>elagolix | 35 days<br>(12 weeks for depot subcutaneous or intramuscular injections) | Not allowed (other than the study drugs) |
| Intrauterine devices | levonorgestrel<br>copper | 56 days | Not allowed |
| Aromatase Inhibitors | anastrozole<br>letrozole | 28 days | Not allowed |
| Anti-Androgens | danazol | 12 weeks | Not allowed |
| Over-the-counter and herbal products/teas with known hormonal activity | plant-based estrogen products<br>“natural” thyroid supplements<br>dihyroepiandrosterone (DHEA) | 1 week | Not allowed |

**Table 5-5 Prohibited Nonhormonal Medications and Windows of Exclusion**

| Drug Class | Excluded Drugs or Examples of Excluded Drugs | Window of Exclusion | |
|---|---|---|---|
| | | During the Run-In Period | During the Study, after Randomization |
| Analgesic Drugs **other** than those specified for use during the study[1] | **Examples:**<br>Acetaminophen/paracetamol (other than any included in a study-specified analgesic)<br>aspirin > 325 mg/day<br>NSAIDSs (other than study-specified NSAID)<br>gabapentin<br>pregabalin<br>carbamazepine<br>metamizole | Not allowed<br>Note: Aspirin ≤ 325 mg per day is allowed. | Not allowed<br>Note: Aspirin ≤ 325 mg per day is allowed if the dose is the same as used during the Run-In Period. |
| Antidepressants<br>New treatment or changed doses of SSRI, SNRI, or TCA antidepressants | **SNRI examples:**<br>duloxetine<br>venlafaxine<br>desvenlafaxine<br>**SSRI examples:**<br>citalopram<br>fluoxetine<br>paroxetine<br>fluvoxamine<br>**TCA examples:**<br>amitriptyline<br>doxepin<br>desipramine<br>nortriptyline | SSRI, SNRIs, TCA allowed if the dose was stable during the 3 months prior to the Run-In Period.<br>New start, dose change or discontinuation of these drugs is not allowed. | SSRI, SNRI, or TCA allowed if given at the same dose as used during the 3 months prior to the Run-In Period.<br>New start, dose change or discontinuation of these drugs is not allowed during the study. Changes made for safety reasons are allowed with approval of the medical monitor. |
| Specific anticonvulsant drugs | **Excluded Drugs:**<br>phenobarbital<br>carbamazepine<br>phenytoin<br>valproic acid<br>primidone<br>**Note**: All other anticonvulsants are allowed | Not allowed | Not allowed |

| Drug Class | Excluded Drugs or Examples of Excluded Drugs | Window of Exclusion | |
|---|---|---|---|
| | | During the Run-In Period | During the Study, after Randomization |
| Agents used to decrease bone mineral density loss | **Examples:**<br>alendronate<br>risedronate<br>zoledronic acid<br>ibandronate<br>calcitonin<br>calcitriol<br>denosumab<br>ipriflavone<br>teriparatide<br>abaloparatide<br>romosozumab<br>strontium ranelate | Not allowed<br>Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction. | Not allowed<br>Note: Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction. |
| Glucocorticoids (systemic)<br>Systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day and epidural or spinal glucocorticoids | **Examples:**<br>prednisone<br>prednisolone<br>dexamethasone | Not allowed<br>Note: Topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous glucocorticoids are allowed without restriction. | Not allowed<br>Note 1: Topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous glucocorticoids are allowed without restriction.<br>Note 2: Short-duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study. |
| P-glycoprotein inducers | **Examples:**<br>avasimibe<br>carbamazepine<br>phenytoin<br>rifampin<br>St. John's wort<br>tipranavir/ritonavir | Not allowed within 2 weeks prior to randomization | Not allowed<br>Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period. |

| Drug Class | Excluded Drugs or Examples of Excluded Drugs | Window of Exclusion | |
|---|---|---|---|
| | | During the Run-In Period | During the Study, after Randomization |
| Moderate and strong P-glycoprotein inhibitors | **Examples:**<br>amiodarone<br>azithromycin[a]<br>captopril[b]<br>carvedilol<br>clarithromycin[a]<br>conivaptan<br>cyclosporin[c]<br>diltiazem<br>dronedarone<br>erythromycin[a]<br>felodipine[d]<br>itraconazole[e]<br>ketoconazole[e]<br>lopinavir/ritonavir[f]<br>quercetin<br>quinidine<br>ranolazine<br>ticagrelort[g]<br>verapamil | Not allowed within 2 weeks prior to randomization (6 months for amiodarone) | Not allowed<br>Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period. |
| Investigational drugs or devices | | Not allowed | Not allowed |

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; SNRI, serotonin norepinepehrine re-uptake inhibitors; SSRI, selective serotonin re-uptake inhibitors; TCA, tricyclic antidepressant
[1]For situations where non-study analgesics may be allowed, see Section 5.7)

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

### 5.11.2. Prohibited Procedures

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

## 6. STUDY ASSESSMENTS AND PROCEDURES

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

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into four periods: Screening Period, Run-In Period, Randomized Treatment Period, and Safety Follow-Up (to assess safety for patients who do not enroll in an open-label extension study); Unscheduled visits may also occur as needed to evaluate patients.

## 6.1. Washout Period

Informed consent may be obtained from the patient up to 90 days prior to the Screening visit to allow for the washout of prohibited medications and to confirm eligibility based on medical record review, including records relating to visualization of endometriosis. The Screening visit procedures may commence up to 1 day prior to the end of the washout period for medications for which a washout or exclusionary period applies (see Section 5.10).

During the Washout period, contact the patient by telephone in approximately 2 weeks following the start of washout, and then, once every approximately 4 weeks to evaluate pain control, to manage pain, if needed, and to reinforce the need for compliance with washout. If during these contacts, it is determined that a clinic visit is needed, then an unscheduled visit should be scheduled. Patients may require an adjustment to their analgesics during this period. There are no protocol restrictions for analgesic use during Washout through the first Screening Visit day. Either study-specified analgesics or other analgesics may be used during the Washout Period.

## 6.2. Screening Period

The full schedule of Screening Period procedures can be found in the Schedule of Activities (Section 1.1).

The Screening visit(s) will occur 1 to 15 days prior to the start of the Run-In Period. The Screening visit should be timed such that Baseline Day 1 will occur during the first 14 days of the menstrual cycle, whenever possible. In general, all Screening visit procedures are expected to be completed during the Screening visit; however, if needed, selected procedures may instead be completed during the Run-In Period (see Section 1.1 for details).

At the Screening visit, prior to all other procedures, other than medical record review, the patient will respond in the electronic tablet to the questions below that evaluate historic endometriosis-associated pain severity (EAPS) to determine if she is eligible to continue screening. Then, the patient will complete the PGA for pain (PGA-screening) in the electronic tablet. The patient's electronic tablet responses on the EAPS must be reviewed in the web portal (TrialManager) to determine her eligibility to continue screening.

**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

The following procedures will be performed for patients who are still eligible:

- Completion of medical history and medication review, if not yet complete*;
- Measurement of vital signs, height, and weight*;
- Blood drawing for central laboratory testing;
- Urine collection for central laboratory testing;
- Urine pregnancy test at the study site*;
- A complete physical examination*;
- Visual acuity testing*;
- A transvaginal ultrasound*;
- 12-lead ECG using a study-supplied ECG machine;
- A gynecologic examination*;
- Papanicolaou test that will be submitted to the central laboratory for reading (if one was not done within 2 years prior to the Screening visit or cannot be documented);
- Endometrial biopsy that will be submitted to the central laboratory for reading;
    - It is strongly recommended that this procedure be completed during Screening, rather than waiting until the Run-In Period. Patients who have a documented and adequate endometrial biopsy from within 6 months prior to Screening are not required to have another biopsy;
- Schedule DXA for bone mineral density assessment at a facility that has been trained by the central radiology vendor for the study. It is recommended that the DXA be completed during Screening, whenever possible, rather than waiting until the Run-In Period;

- Schedule a mammogram for women ≥ 39 years at the Screening visit (if one was not done within 6 months prior to the Screening visit or cannot be documented);
- Training and Dispensation of the eDiary 1 day prior to the start of the Run-In Period;
- Paper Questionnaires in the following order: PGA for dysmenorrhea, PGA for NMPP, and PGA for function;
- Dispensation and/or prescription for study analgesic medications (see Appendix 8). Patient must have their supply of medications prior to the start of the Run-In Period;
- Update the patient's status in the IVRS/IWRS as being in the Run-In Period and receive the Run-In Kit #s for study drug allocation;
- Patient must have their supply of medications prior to the start of the Run-In Period;
- Dispensation of Run-In Period study drug;
- Record any serious adverse events or adverse event related to study procedures.

*Patients who qualify based on results of these procedures may proceed to Run-In Day 1 (R1).

Scheduling should be done as early as possible to accommodate the time for central reading of the bone mineral density and endometrial biopsy.

## 6.3. Run-In Period

The full schedule of Run-In Period procedures can be found in the Schedule of Activities (Section 1.1).

If needed, for logistical reasons (eg, need for repeat endometrial biopsy) or due to an insufficient number of dysmenorrhea scores during Run-In Days R1-R35, the Run-In Period may be increased by an additional up to 35 days (ie, through Run-In Day R70) with Sponsor/designee approval. Patients continuing in Run–In beyond Day R42 may require additional study drug to be dispensed to avoid interruption of drug during the Run-In Period. Contact the Sponsor/designee as soon as possible if there is an issue that may preclude randomization within 8 days following Day R35. Transmission of eDiary data through Day R35 should still be done, even if the sponsor has granted an extension of the Run-In Period.

### 6.3.1. Run-In Days R1 to R7

- Initiate Run-In period study drug treatment on Day R1.
- Within 4 to 7 days of the start of the Run-In Period, contact the patient by telephone to reinforce the eDiary and rescue analgesic medication instructions. Stress the importance of compliance.
- If needed, confirm or convey the dates for the mammogram and DXA.
- Record any adverse events and serious adverse events.
- Record any changes to concomitant medications.

### 6.3.2. Run-In Days R1 to End of Run-In

- Review eligibility.

- If it was not completed during Screening, complete the endometrial biopsy as early as possible during the Run-In Period.

- Confirm that mammogram (if needed) and DXA have been completed.
- Schedule the Baseline Day 1 visit. Baseline/Day 1 should be scheduled to occur no later than the day after Day R42 and timed to occur during Days 1 through 14 of the menstrual cycle whenever possible. If a Sponsor-approved window extension has been granted (see footnote c), then Baseline Day 1 should be scheduled to occur no later than 1 day after the end of that window.
- Record any adverse events and serious adverse events.
- Record any changes to concomitant medications.

### 6.3.3. Run-In Period Days R36 to End of Run-In

- As soon as feasible after the Day R35 eDiary has been completed, ensure that the patient's eDiary data have been transmitted successfully and that there are at least 24 days of scores during the period Day R1 through R35 and the PGIC for NMPP on Day R33 to R35 has been completed.
- The sponsor will determine eligibility for the patient based on the transmitted eDiary pain scores and will inform the site of the patient's eligibility status within 7 days.
- If the patient is eligible, confirm the Baseline Day 1 visit with the patient.
- The patient should be reminded to continue to record daily eDiary scores.
- The patient should be reminded to continue Run-In period study drug until the day before the Baseline Day 1.
- Record adverse events and serious adverse events.
- Record any changes to concomitant medications.

### 6.3.4. Re-screening

Patients who did not meet enrollment criteria may be re-screened with approval of the medical monitor. For patients who start re-screening within 10 weeks of Run-In Day R1, transvaginal ultrasound, endometrial biopsy, and DXA do not need to be repeated, if performed previously.

## 6.4. Re-testing

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

## 6.5. Randomized Treatment Period (Baseline Day 1 to Week 24)

The full schedule of Randomized Treatment Period procedures can be found in the Schedule of Activities (Section 1.1).

At the Baseline Day 1 visit, patients will be randomized to one of the 3 study treatment groups (see Section 5.3). Patients will take their randomized study treatment once daily, beginning on the day of the Baseline Day 1 visit and continuing through the ***day prior to*** the Week 24 visit. Patients will continue completing their eDiary on a daily basis. Study visits will occur every 4 weeks through the end of Week 24 during the Randomized Treatment Period. Safety monitoring, including adverse event collection, signs and symptoms directed physical examination, ECGs, clinical laboratory tests, pregnancy tests, and review of concomitant medications will occur at each visit. Bone densitometry will occur at the Week 12 and 24 visits. Study drug and eDiary compliance will be reviewed and reinforced at each visit. Accountability for study drug will be performed at each visit. Instructions for analgesic medication usage will be reinforced at each visit. Refer to the Schedule of Activities in the synopsis (see Section 1.1) for information about study procedures during the Randomized Treatment Period.

The Week 24 visit procedures that require central reading (ie, bone densitometry) and visual acuity testing should be done as early as possible in the Week 24 visit window (-10 days to +20 days). Schedule the final Week 24 visit to occur when the results of the above testing are available.

Questionnaires administered on the electronic tablet and on paper should occur before any other study procedures are performed at each visit. When both electronic tablet and paper questionnaires are required at a visit (ie, Baseline Day 1, Week 12, and Week 24), the electronic questionnaires should be done first. The order in which the electronic tablet and paper questionnaires should be administered are as follows:

- Electronic tablet questionnaires (in the order they appear in the tablet)
- Paper questionnaires
  - PGA for dysmenorrhea
  - PGA for NMPP
  - PGA for function
  - EHP Work Domain [Baseline Day 1 and Week 24 only]

Sites should try to schedule patient visits in the morning.

On the Baseline Day 1 visit and Week 24/Early Termination visit, patients should be instructed not to eat or drink (other than water) for at least 8 hours prior to their clinic visit.

On other visits during which study drug will be administered in the clinic (see Section 1.1), patients should be instructed not to eat or drink (other than water, tea, or coffee) prior to their clinic visit if the appointment is in the morning. If the appointment is later in the day, patients should not eat or drink (other than water, tea, or coffee) for at least 2 hours before the appointment and also not eat or drink (other than water, tea, or coffee) for at least 1 hour after the in-clinic administration of the study drug.

## 6.6. Continuation into Extension Study

It is expected that most patients will enter the 28-week extension study (MVT-601-3103), which will be conducted under a separate protocol. Patients will provide separate informed consent under the MVT-601-3103 protocol to participate in the extension study. During the extension

study, all patients will receive relugolix 40 mg co-administered with 1.0 mg estradiol / 0.5 mg norethindrone acetate. Prior to the transition to the extension study, patients must be deactivated within the IVRS/IWRS to indicate their completion of the parent study. They must also be transitioned within the eDiary and tablet device from the parent study to the extension study.

## 6.7. Early Termination Visit and Follow-Up Visit

Refer to the Schedule of Activities (see Section 1.1) for individual study visit procedures during the Early Termination visit and Follow-Up visit.

All patients withdrawing from the study prior to Week 24 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 24; however, for patients whose last dose of study drug is during Week 6 or earlier, the endometrial biopsy does not need to be performed. This procedure may be performed, however, at the investigator's discretion, if it aids in follow-up of an ongoing adverse event. The DXA is not required at the Early Termination visit in patients whose last dose of study drug was during Week 6 or earlier or within 4 weeks after completion of the Week 12 scan.

All patients who do not wish to or who are not eligible to enroll in the extension study (MVT-601-3103), will have a Follow-Up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first. This visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, 12-lead ECG, and return of menstruation.

Patients who withdraw early from this study will undergo the Follow-Up visit approximately 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first.

## 6.8. Additional Safety Follow-Up Procedures

For patients not continuing into the extension study (MVT-601-3103), additional safety procedures are required in some circumstances as described below. These procedures will be performed during unscheduled visits.

- Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.
- Patients who have had a bone mineral density loss of > 2% at the lumbar spine (L1-L4) or total hip at their Week 24/Early Termination visit or most recent study scan relative to baseline (Run-In Period) will undergo another bone densitometry 6 months (± 1 month) after discontinuation of study drug to evaluate recovery and will be contacted to obtain information about medications and conditions (eg, pregnancy, hyperparathyroidism, hypothyroidism, etc) that might affect bone mineral density through the time of the repeat bone densitometry. The repeat bone densitometry will be submitted for central reading.

- Patients whose presenting visual acuity score at Week 24 /Early termination has decreased by 10 or more points from the Screening/Run-In Period score should be referred to an ophthalmologist for a diagnostic evaluation. A copy of the ophthalmology consultation must be submitted to the sponsor.

## 6.9. Unscheduled Visits

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

## 6.10. Study Procedures

### 6.10.1. Efficacy-Related Procedures

#### 6.10.1.1. Transvaginal Ultrasound

Transvaginal ultrasound (with or without saline or gel contrast) is performed to help exclude any other uterine or pelvic pathology that may be contributing to pelvic pain. To avoid inter-observer and inter-device variations, a single operator will be assigned to a patient and will perform each of the ultrasound scans using the same device as much as possible. The ultrasound will be read locally.

#### 6.10.1.2. Pharmacodynamics Sample Collection

Blood samples for the pharmacodynamic analysis of serum LH, FSH, estradiol, and progesterone will be collected pre-dose at the visits indicated in the study Schedule of Activities (see Section 1.1). These pharmacodynamic samples will be analyzed at a central laboratory. To maintain blinding, concentrations of these hormones will be reported to other vendors, and sponsor personnel only after database lock and unblinding. These results will not be shared with the sites at any time.

#### 6.10.1.3. Patient eDiary

All women enrolled in the study will be provided with a device with an application for a patient eDiary (See Appendix 2), along with detailed instructions for its use. Patients will complete

daily eDiary entries including NRS pain scores, menstruation information, analgesic drug use, date and time of study drug administration, and sB&B scale scores.

The site should review the eDiary data at every visit.

#### 6.10.1.4. Endometriosis Health Profile - 30

The EHP-30 is used to evaluate the functional impact and the quality of life of patients with endometriosis (see Appendix 4). Patients will complete the EHP-30 questionnaire at the site at the Baseline Day 1 visit, Week 12 visit, and Week 24 visit before other types of study procedures, such as blood draws and physical examinations, are performed. The EHP-30 will be completed on a tablet device at the study site.

#### 6.10.1.5. European Quality of Life Five-Dimension Five-Level Scale

The EQ-5D-5L is a standardized instrument for use as a measure of health outcomes (see Appendix 6). Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression are each assessed on a 5-level categorical scale.

Patients will complete the EQ-5D-5L questionnaire at the site at the Baseline Day 1 visit and the Week 24 visit before other types of study procedures, such as blood draws and physical examinations, are performed. The EQ-5D-5L will be completed on a tablet device at the study site.

#### 6.10.1.6. Patient Global Assessment and Patient Global Impression of Change

These simple questions are used by the patient to qualitatively describe severity of pain or effects on function (PGA) or impression of change in pain severity (PGIC) (see Appendix 3) on a schedule described in the Schedule of Activities (Section 1.1). Patients should answer these questions before other types of study procedures, such as blood draws and physical examinations, are performed. At the Screening visit, the Endometriosis-Associated Pain Severity (see boxed item in Section 6.2) will be completed prior to the PGA. The PGA for pain severity and the PGIC will be completed on a tablet device at the study site. The PGAs for dysmenorrhea, NMPP, and function will be completed on a paper questionnaire at the study site.

#### 6.10.1.7. Endometriosis Health Profile Work Domain

This 5-question paper questionnaire will be completed by the patient to describe the effects of endometriosis on their work (Appendix 5). Patients will complete the EHP Work Domain questionnaire at the site at the Baseline Day 1 visit and Week 24 visits before other types of study procedures, such as blood draws and physical examinations, are performed.

#### 6.10.1.8. Status of Menstruation Recovery

If the patient does not continue into the extension study (MVT-601-3103), and the first menstruation after the end of study treatment administration is observed before the Follow-Up visit, the date of onset of the first menstruation is recorded in the electronic case report form

(eCRF). Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted again by telephone (see Section 6.8).

#### 6.10.1.9. Pharmacogenomics Sample Collection

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

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

#### 6.10.1.10. Genomics Sample Collection

For investigating endometriosis disease markers, samples of blood will be collected for DNA and micro-ribonucleic acid (miRNA) analyses, unless precluded by local law or regulations. All patients will be eligible for collection of the genomics samples, however, the samples may only be obtained and stored from patients who provide a separate informed consent form for genomics sample collection. Patient participation in the genomics research is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

Patients can request their samples to be destroyed at any time. Genomics samples should not be collected from any patient who has received a bone marrow transplant or whole blood transfusion within 6 months before sample collection. Refer to the Study Reference Manual for directions on collecting, handling, and storage of genomics samples.

### 6.10.2. Safety-Related Procedures

#### 6.10.2.1. Vital Signs

Vital signs, including blood pressure, respiratory rate, heart rate, and temperature, should be measured in the seated position after 5 minutes of rest.

#### 6.10.2.2. Weight and Height

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

#### 6.10.2.3. Physical and Gynecologic Exams and Papanicolaou Test

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent (ie, post-randomization) physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. The gynecologic examinations will include breast and pelvic exams. A Papanicolaou test must be conducted for women without an available test result from within 2 years prior to the Screening visit. Re-measurement should be performed for inadequate samples or potential false-positive results.

#### 6.10.2.4. Endometrial Biopsy

An endometrial biopsy will be performed using an endometrial suction curette (eg, Pipelle®) and submitted to the central laboratory for reading. Local anesthetics may be given for endometrial biopsies according to the investigator's discretion. If the biopsy is inadequate for diagnosis, it should be repeated and sample submitted to the central laboratory. If the second specimen is also inadequate, the patient is not eligible for the study.

#### 6.10.2.5. Visual Acuity

Presenting visual acuity must be assessed with the supplied study eye chart. If the patient uses corrective lenses, she should wear her usual prescription glasses or contact lenses during the assessment, and the same prescription lenses should be worn during the assessment, and subsequent visual testing. Perform the visual acuity testing using the entire eye chart. Do not stop at a visual acuity of 100 – continue as far as the patient can go per the testing instructions (see Study Reference Manual for additional details).

Patients whose presenting visual acuity score is 90 or lower at the Screening visit should be encouraged to obtain a diagnostic evaluation from an eye care provider, ie, an ophthalmologist or an optometrist. Any findings (ie, diagnoses) from the eye examination should be recorded as medical history.

If a treatment or correction was made to treat visual acuity (eg, stronger eyeglasses) prior to the first dose of study drug, repeat the presenting visual acuity testing with the new correction (eg, with the new corrective lenses). For patients whose presenting visual acuity score has declined at the Week 24/Early Termination visit, please see Section 6.8 for follow-up requirements.

#### 6.10.2.6. Electrocardiograms

ECGs (12-lead) will be obtained at the time points described in the Schedule of Activities (Section 1.1). ECGs will be measured using standardized equipment provided by central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal.

The investigator or sub-investigator will judge if any of the findings are clinically significant. The Baseline Day 1 QTcF may be assessed locally for purposes of eligibility determination.

#### 6.10.2.7. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Study Laboratory Manual and the protocol Schedule of Activities (see Section 1.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the Patient ID number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

The samples collected for clinical laboratory tests are listed in Table 6-1.

**Table 6-1 Clinical Laboratory Tests**

| Chemistry | Hematology | Urinalysis |
|---|---|---|
| Potassium | White blood cell count | Protein |
| Chloride | White blood cell differential | Glucose |
| Bicarbonate | Red blood cell count | Blood |
| Blood urea nitrogen | Hemoglobin | Urobilinogen |
| Creatinine | Hematocrit | Bilirubin |
| Glucose | Mean corpuscular volume | Color and clarity |
| Calcium | Platelet count | pH |
| Phosphate | Red blood cell morphology | Leucocyte esterase |
| Magnesium | | Ketones |
| Sodium | | Nitrite |
| Albumin | | Specific gravity |
| Creatinine kinase | | Urine Microscopy |
| Hemoglobin A1c | | |
| Bilirubin total | | |
| Alanine aminotransferase | | |
| Aspartate aminotransferase | | |
| Gamma-glutamyl transferase | | |
| Alkaline phosphatase | | |
| **Lipids** | **Serology** | **Pregnancy** |
| Total cholesterol | Hepatitis A antibody | Pregnancy test (human chorionic gonadotropin) |
| Low density lipoprotein | Hepatitis B surface antigen | |
| High density lipoprotein | Hepatitis B core antibody | |
| Triglycerides | Hepatitis C antibody | |

| Hormones | | |
|---|---|---|
| Thyroid-stimulating hormone<br>Prolactin<br>Luteinizing hormone<br>Follicle-stimulating hormone<br>Estradiol<br>Progesterone<br>25 (OH) vitamin D | | |

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

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

All laboratory tests with values that are considered abnormal and clinically significant during participation in the study or within 30 days after the last dose of study drug should be repeated until the values return to normal, baseline, or have stabilized. Abnormal values, determined to be clinically significant, should be reported as adverse events.

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

#### 6.10.2.8. 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 (Section 1.1). The scans will be read by the central radiology laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient. The central radiology laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central radiology laboratory over the course of the study. Investigators will be notified if a patient experiences a bone mineral density loss from baseline of 7% or more at any of the anatomical sites assessed during the study. In this case, it is at the investigator's discretion to consider the patient's status and determine future management. Detailed instructions for DXA scanning are provided in the Study Reference Manual.

Please see Section 6.8 for follow-up of patients whose bone mineral density has decreased by > 2% at the lumbar spine (L1-L4) or total hip at the Week 24/Early Termination visit or most recent study scan relative to Baseline (Run-In Period).

### 6.11. Biological Sample Retention and Destruction

Biological samples present at the conclusion of this study may be retained in storage by the sponsor for a period up to 10 years for purposes of this study. Samples collected for pharmacogenomics and genomics testing (see Sections 6.10.1.9 and 6.10.1.10) will be stored frozen at an appropriate vendor facility identified by the sponsor.

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

## 7. SAFETY CONSIDERATIONS

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

### 7.1. Adverse Event Definitions

#### 7.1.1. Adverse Event

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

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

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

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

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

Adverse events that occur during the study should be evaluated by the investigator and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). Episodic adverse events, such as vomiting, or those that occur repeatedly over a period of consecutive days are "intermittent". All other events are "continuous". Additional information on detecting, documenting, and reporting adverse events and serious adverse events are provided below.

### 7.1.2. Serious Adverse Event

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

a. Results in death;

b. Is life-threatening;

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

c. Requires hospitalization or prolongation of existing hospitalization;

   NOTE: In general, hospitalization signifies that the patient has been detained at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an adverse event.

d. Results in persistent or significant disability/incapacity;

   NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

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

e. Is a congenital anomaly/birth defect;

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

## 7.2. Adverse Event Reporting

The reporting of serious adverse events by the sponsor (Myovant Sciences GmbH) to regulatory authorities is a requirement and each authority has a timetable for reporting these events based upon established criteria. Likewise, it is the responsibility of the investigator to report serious adverse events to their local Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

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

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

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

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

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

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

### 7.2.1. Adverse Event Reporting Period

Adverse events will be collected from the time the first dose of single-blind study drug is administered in the Run-In Period through the double-blind Randomization Treatment Period and until the Follow-Up visit (approximately 30 days after the last dose of study drug) or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). For patients entering the extension study, adverse event collection for this study will end at the Week 24 visit. Study procedure-related adverse events will be collected from the signing of the informed consent form.

Serious adverse events will be collected from the signing of the informed consent form until the safety follow-up visit (approximately 30 days after the last dose of study drug). For patients entering the extension study, serious adverse event collection for this study will end at the Week 24 visit. Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

With the exception of events that are considered related to study screening procedures, (which are to be recorded as adverse events), events occurring between signing of the informed consent form and the first dose of study drug will be recorded as medical history and in the patient's clinical record for any patient who continues to meet eligibility criteria and proceeds to dosing with study drug.

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

## 7.3. Assigning Causal Relationship to Study Drug

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

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

All adverse events, whether or not related to study drug, must be fully and completely documented on the adverse event page of the eCRF and in the patient's clinical record. In the event a patient is withdrawn from the study because of an adverse event, it must be recorded on the eCRF as such.

## 7.4. Assigning Severity Rating for Adverse Events

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

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

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

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

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

## 7.5. Adverse Events of Clinical Interest Reporting

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

Any ALT or AST elevation of this degree or greater occurring during the Randomized Treatment Period or the Follow-Up visit should be reported to the sponsor using the Serious Adverse Event Form **within 24 hours of the study site personnel's knowledge of the event** (see Section 7.6), **even if the event does not meet SAE criteria**. Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 7, **even if the event does not meet SAE criteria**.

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

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

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

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

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

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

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

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

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

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

## 7.6. Serious Adverse Event Reporting

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

The contact information for submission of serious adverse events, adverse events of clinical interest (defined in Section 7.5), and events of overdose is available on the Serious Adverse Event report form and is as follows:

**Send completed Safety Report Forms to IQVIA RDS Inc. (formerly QuintilesIMS):**

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

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

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

The initial report should include:

- Study number (MVT-601-3102);
- Site address and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity);
- Causal relationship to the study drug.

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

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

## 7.7. Study Drug Overdose Management

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

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

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

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

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

## 7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit. The investigator must inform the patient of her right to receive treatment information. If the patient chooses to receive unblinded treatment information, the individual blind should be broken and the treatment assignment provided to the patient. The study team will remain blinded to the patient's treatment assignment.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment (blinded or unblinded, as applicable).

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

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

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

Section 6.10.1.10 details the requirements for measurement of safety parameters including vital signs, physical and gynecologic examinations, clinical laboratory tests, ECGs, and bone mineral density.

## 7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on endometriosis-associated pain. Low-dose hormonal add-back therapy with estradiol and norethindrone acetate will be evaluated for maintenance of bone mineral density during treatment with relugolix.

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

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

**Table 7-2 Protocol Risk Assessment and Mitigation Strategies**

| Potential Risk of Clinical Significance | Mitigation Strategy | |
|---|---|---|
| | **Impact on Eligibility** | **Monitoring and Withdrawal Criteria** |
| Bone Mineral Density<br>Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy. | Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density. | Bone mineral density will be monitored per the Schedule of Activities and all fractures will be reported as adverse events. |
| Drug Interactions | Exclusion of co-administration of P-glyoprotein inhibitors/inducers. | Collection of adverse events. |
| QTc Prolongation<br>Negative Thorough QT/QTc clinical study. | Empiric exclusion of baseline QTcF > 470 msec. | 12-lead ECG will be monitored per the Schedule of Activities; withdrawal for QTcF > 500 msec. |

| Potential Risk of Clinical Significance | Mitigation Strategy | |
|---|---|---|
| | **Impact on Eligibility** | **Monitoring and Withdrawal Criteria** |
| Hepatic Enzymes Increase<br>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 function tests, also referred to as liver tests as these are not solely measuring liver function, are considered adverse events of clinical interest in this study. | Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN | Abnormal liver tests (AST or ALT > 3 x ULN) that develop during the randomized study treatment period will be reported within 24 hours of study personnel awareness. |
| Phospholipidosis<br>Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies. | Patients with significant underlying medical conditions are excluded. | Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events; visual acuity will be checked at the beginning and end of the study. |
| Metabolic Changes<br>Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix. | Exclusion criteria for current medical history of cardiovascular disease. | Fasting lipids and glucose will be monitored during the study. |
| Reproductive Toxicity | Premenopausal compliance with specified acceptable nonhormonal contraception; exclusion of pregnant and lactating women. | Monthly pregnancy testing; immediate withdrawal for pregnancy. |

| Potential Risk of Clinical Significance | Mitigation Strategy | |
|---|---|---|
| | **Impact on Eligibility** | **Monitoring and Withdrawal Criteria** |
| Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg)<br>Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy. | Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, and pregnancy are excluded. A mammogram, Papanicolaou test, physical examination, clinical chemistries, and 12-lead ECG will be performed prior to enrollment. | Clinical chemistries assessing liver function, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit. |

# 8. DATA QUALITY ASSURANCE

## 8.1. Clinical Procedures

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

## 8.2. Monitoring

This study will be monitored by the sponsor (or designee) in accordance with current Good Clinical Practice (GCP) regulations. By signing this protocol, the investigator grants permission to Myovant Sciences GmbH (or designee) and appropriate regulatory authorities to conduct on-site monitoring of all appropriate study documentation. In order to assure the accuracy of data collected in the eCRF, it is mandatory that representatives of the sponsor (or designee) have access to original source documents (eg, patient records, patient charts, and laboratory reports). During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality. A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various records of the study. It will be the study monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, correctness and accuracy of all eCRF entries, and to meet with the investigator to discuss study progress and compliance with the protocol and GCP. The study monitor should have access to

laboratory test results and any other source records and data needed to verify the entries on the eCRF. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved. For this study, patient data will be entered into a sponsor-approved electronic database and combined with data provided from other sources in validated datasets then transmitted electronically to the sponsor (or designee).

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

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

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

# 9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

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

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

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

The study may be closed pending selected contingent safety procedures conducted after the last patient's Week 24/Early Termination or Follow-Up visit. After the study is closed, any pending required follow-up testing of bone mineral density or for menstruation recovery beyond the Follow-Up visit in patients not proceeding into the extension study will be captured and reported.

The single, final analysis of all efficacy and safety data will occur after approximately 600 patients have been randomized and have had the opportunity to be followed for 24 weeks of study treatment or through the 30-day safety follow-up visit (if not enrolling in the extension study, MVT-601-3103).

## 9.1. Randomization Methods

Central randomization will be used and treatment allocation will be 1:1:1 to relugolix plus low-dose hormonal add-back therapy (Group A), relugolix monotherapy plus placebo followed by relugolix plus low-dose hormonal add-back therapy (Group B), and placebo (Group C) (see Table 5-3 for treatment group details). Randomization will be stratified by the following factors:

- Geographic Region: North America versus Rest of World; and

- Time since surgical diagnosis of endometriosis: < 5 years versus ≥ 5 years.

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

## 9.2. Analysis Populations

The modified Intent-to-Treat (mITT) Population will consist of all patients randomized to treatment who have taken at least 1 dose of randomized study treatment. This will be the primary population used for the efficacy analysis.

The Per-Protocol Population will consist of those members of the mITT Population who have no relevant major protocol violations, defined as a subset of all major protocol violations (details will be provided in the Statistical Analysis Plan). The Per-Protocol Population will not be analyzed if this population comprises more than 95% or less than 50% of the mITT Population. This population will be used for confirmatory analysis of the primary efficacy endpoint. The Per-Protocol Population will be identified prior to unblinding the study treatment assignments.

The primary population for safety analyses will be the Safety Population, which will consist of all patients who are randomized and took at least 1 dose of randomized study drug treatment.

## 9.3. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the mITT Population according to the randomized treatment assignment, and stratified analyses will be stratified by the randomization stratification factors. If the group of patients from any of the individual randomization stratification factors (eg, patients with a time from diagnosis of endometriosis < 5 years) comprises less than 10% of the entire mITT population, this stratification factor will be ignored for stratified analyses.

### 9.3.1. Co-primary Efficacy Endpoints

The study has two co-primary efficacy endpoints comparing Group A versus Group C:

- Proportion of responders at Week 24/End of Treatment (EOT) pain assessment period, based on the dysmenorrhea NRS scores recorded in a daily electronic diary and use of rescue analgesics; and
- Proportion of responders at Week 24/EOT pain assessment period based on the NMPP NRS scores as recorded in a daily electronic diary and use of rescue analgesics.

A responder at Week 24/EOT is defined as a patient who had a reduction from Baseline of the determined threshold (or clinically meaningful difference) or greater from Baseline in pain and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain during the Week 24/EOT pain assessment period compared with the use in the Baseline pain assessment period.

The Baseline pain assessment period is defined as the period from the date of the first dose of placebo in the Run-In Period through the day prior to the date of the first dose of randomized

study drug treatment The Week 24/EOT pain assessment period is defined as the last 35 calendar days immediately prior to and including the last dose of randomized study drug treatment.

Pain data collected in the Baseline pain assessment period will be used as baseline. The Baseline value for dysmenorrhea is defined as the mean NRS scores over the days with menses during the Baseline pain assessment period. The Baseline value for NMPP is defined as the mean NRS scores over the days without menses during the Baseline pain assessment period. The Baseline value for total dose counts is defined as the mean daily dose counts taken during the Baseline pain assessment period multiplied by 35.

The clinically meaningful difference will be determined for NMPP and dysmenorrhea separately (see the Statistical Analysis Plan for details). The anchor-based methods (using PGA for dysmenorrhea and PGA for NMPP as anchors) supplemented with both cumulative distribution function (CDF) and probability density function (PDF) curves will be considered as primary methods to derive the meaningful pain reduction thresholds to be used to define a responder.

Determination of the meaningful pain reduction threshold using PGIC as the anchor will also be explored as supportive.

A patient will be considered a non-responder if there is an increase in the use of rescue analgesic medications during the Week 24/EOT pain assessment period compared with the Baseline pain assessment period. Details will be provided in the Statistical Analysis Plan.

#### 9.3.1.1. Primary Analysis

The primary hypotheses for each of the co-primary efficacy endpoints to be tested in this study are the following:

1. Relugolix (Group A) is superior to placebo (Group C) with respect to proportion of responders at the Week 24/EOT pain assessment period based on the dysmenorrhea NRS scores recorded in a daily electronic diary and use of rescue analgesics:

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

2. Relugolix (Group A) is superior to placebo (Group C) with respect to proportion of responders at the Week 24/EOT pain assessment period based on the NMPP NRS scores recorded in a daily electronic diary and use of rescue analgesics:

   Null hypothesis H02: $\pi^R \leq \pi^P$ vs Alternative hypothesis Ha2: $\pi^R > \pi^P$

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

The co-primary endpoints of dysmenorrhea and NMPP responder rates will be evaluated using the mITT Population. A logistic regression model will be used to compare relugolix Group A with placebo Group C for each endpoint. The responder status will be the dependent variable; treatment will be the main effect, and Baseline pain scores and stratification factors will be the covariates. The study will be considered positive if both co-primary endpoints are statistically significant with 2-sided p-values < 0.05.

In addition, the difference in responder rates between Group A and C for each co-primary endpoint will be estimated and displayed along with their 2-sided 95% confidence intervals.

#### 9.3.1.2. Subgroup Analyses

Subgroup analyses of the co-primary efficacy endpoints comparing Group A versus Group C will be performed to determine whether treatment effects are consistent across clinically meaningful subgroups. The difference in responder rates and their 95% confidence intervals will be displayed in a forest plot. Subgroups will include but not be limited to the following: geographic region (North America, Rest of World) and time from diagnosis of endometriosis to study entry (< 5 years, ≥ 5 years) as well as other subgroups based on Baseline pain severity, age, and race. Details are provided in the Statistical Analysis Plan.

#### 9.3.1.3. Sample Size Justification

The following assumptions are used to determine the sample size for this study:

- 2-sided type I error rate: 0.05;
- Randomization: 1:1:1;
- Responder rate for Group C: 30-35%;
- Difference in responder rates between Group A and Group C: 20%;
- Dropout rate: 20%.

Assuming a dropout rate of 20%, approximately 200 women in relugolix Group A and 200 women in placebo Group C will provide at least 95% power at a 2-sided 0.05 significance level to detect a 20% difference in responder rates between Group A and Group C for each individual co-primary endpoint. This will provide an overall power of at least 90% for the study to detect a 20% treatment difference for both co-primary endpoints simultaneously. The responder rate for Group C is assumed to be between 30 and 35%. The proposed fixed sample size of 400 patients in Groups A and C is adequate to detect the target difference of 20% in responder rates between the two groups. It is calculated considering overall responder rates of close to 50% from which the maximum sample size is reached. With an additional 200 women in relugolix Group B, the total sample size will be approximately 600 women.

The assumed responder rate of 30 to 35% for Group C is within the range of responder rates (approximately 25 to 40%) observed in similar phase 3 endometriosis trials [Taylor, 2017]. The sample size and power calculations are based on the chi-squared test and were performed using the software package *nQuery* 4.0.0.0 (Statistical Solutions Ltd.).

### 9.3.2. Secondary Efficacy Endpoints

- Change from Baseline at Week 24/EOT in the EHP-30 Pain Domain scores in the relugolix 40 mg group co-administered with low-dose hormonal add-back therapy for 24 weeks versus placebo;

The change at Week 24/EOT from Baseline in EHP-30 Pain Domain comparing Group A and Group C is a key secondary endpoint to which Type 1 error protection will be extended.

To assist in score interpretation, a meaningful within-patient score change threshold for the EHP-30 pain domain will be determined using a similar approach as that for the primary endpoint. A responder at Week 24/EOT based on EHP-30 pain domain scores is defined as a patient who had a reduction of the determined threshold or greater from Baseline using PGA for function as the anchor. Proportion of responders at Week 24/EOT based on EHP-30 Pain Domain scores is a secondary endpoint;

The following secondary endpoints will be assessed comparing Group A with Group C. The Statistical Analysis Plan will specify to which additional secondary endpoints Type 1 error protection will be extended.

- Change from Baseline to Week 24/EOT in the mean dysmenorrhea NRS score;
- Change from Baseline to Week 24/EOT in the mean NMPP NRS score;
- Change from Baseline to Week 24/EOT in the severity scores on the PGA for dysmenorrhea
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 24/EOT;
- Change from Baseline to Week 24/EOT in the severity scores on the PGA for NMPP.
- Proportion of patients who are better or much better on the PGIC for NMPP at Week 24/EOT;
- Change from Baseline to Week 24/EOT in the mean dyspareunia NRS scores.
- Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 24/EOT;
- Change from Baseline to Week 24/EOT in the mean dyspareunia functional impairment on the sB&B scale;
- Change from Baseline to Week 24/EOT in severity scores on the PGA for pain;
- Proportion of responders at Week 24/EOT based on EHP-30 Pain Domain scores;
- Change from Baseline to Week 24/EOT in function impairment on the PGA for function;
- Change from Baseline to Week 24/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
- Change from Baseline to Week 24/EOT in the mean dysmenorrhea functional impairment on the sB&B scale;
- Change from Baseline to Week 24/EOT in the mean NMPP functional impairment on the sB&B scale.

The following secondary endpoints will be assessed comparing Group B with Group C:

- Proportion of responders at the Week 24/EOT pain assessment period, based on their dysmenorrhea NRS scores recorded in a daily eDiary;
- Proportion of responders at the Week 24/EOT pain assessment period, based on their NMPP NRS scores recorded in a daily eDiary
- Change from Baseline at Week 24/EOT in the EHP-30 Pain Domain scores.
- Proportion of responders at Week 24/EOT based on EHP-30 Pain Domain scores.

#### 9.3.2.1. Secondary Efficacy Endpoint Analyses

If the treatment effects for both co-primary endpoints are statistically significant each at 2-sided 0.05 alpha level, the key secondary endpoint of change from Baseline at Week 24 in the EHP-30 Pain Domain scores will be tested comparing the relugolix Group A versus placebo Group C at a 2-sided 0.05 alpha level. The comparison will be performed using a mixed model repeated measures approach with treatment, randomization stratification factors, and treatment by visit interaction included as fixed effects and baseline value included as a covariate and an unstructured covariance. The dependent variable (change from Baseline) for each patient at each visit will be calculated based on the visit windows specified in the Statistical Analysis Plan. Based on this model, the difference in least squares means of change from Baseline between the two groups and corresponding 95% CI and p-value will be presented at Week 24 comparing Group A with Group C.

If this key secondary endpoint is positive, additional secondary efficacy endpoints to which Type 1 error protection will be extended will be tested comparing Group A with Group C using a closed testing procedure to control the familywise error rate at a 2-sided alpha level of 0.05. The details of the closed testing procedure will be provided in the Statistical Analysis Plan, which will be finalized prior to unblinding the trial.

For endpoints evaluating the change from Baseline to Week 24/EOT, treatment comparisons will be performed using a mixed model repeated measures approach with treatment, randomization stratification factors, and treatment by visit interaction included as fixed effects and Baseline value included as a covariate. The dependent variable (change from Baseline) for each patient at each visit will be calculated based on visit windows specified in the final Statistical Analysis Plan. In addition, descriptive statistics will be provided by treatment group and by visit.

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

The daily average sB&B scores for each patient during a specific pain assessment period will be on a continuous scale for the secondary endpoints involving sB&B items with the categories as follows: none = 0, mild = 1, moderate = 2, severe = 3.

Dyspareunia analyses will be performed only in patients who had vaginal sexual intercourse during both the Baseline pain assessment and Randomized Treatment Periods.

The comparison of Group B versus Group C with respect to the responder rates for dysmenorrhea and NMPP as well as the change from Baseline at Week 24/EOT in the EHP-30 Pain Domain scores will be performed in a similar fashion to that for the co-primary efficacy analyses comparing Group A versus Group C described above.

## 9.4. Pharmacodynamic Analyses

Pharmacodynamics analyses will be described in the Statistical Analysis Plan.

## 9.5. Safety Analyses

Safety analyses will be conducted using the Safety Population and summarized by treatment group as treated. The treatment-emergent period will be defined as the period of time from the first dose date and time of the randomized study drug treatment through 30 days after the last dose of study drug, or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, or the date and time of the first dose of open-label extension (MVT-601-3103) study drug, whichever occurs first. Safety will be assessed through summaries of adverse events, the frequency of treatment discontinuations due to adverse events, laboratory evaluations, and bone densitometry results.

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

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE, will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the Baseline versus post-baseline results. All data will be listed and summarized by visit. The change from Baseline to each post-baseline study visit will be presented by treatment group for each laboratory test.

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

ECGs will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

Bone mineral density will be determined by the central radiology laboratory at the femoral neck, lumbar spine (L1-L4), and total hip. Values at Baseline, Week 12, and Week 24 visits will be summarized by treatment group along with the absolute and percent changes from Baseline and associated 95% confidence intervals. The number and percentage of patients meeting a bone mineral density decline of at least 7% by body area (lumbar, total hip, and femoral neck) will be presented with 95% confidence intervals by treatment group.

To support the inclusion of add-back therapy in the treatment regimen, the safety endpoint of mean percent change from Baseline in bone mineral density lumbar spine at Week 12 will be analyzed using pooled data from the two replicate studies (MVT-601-3101 and MVT-601-3102) with a formal comparison of Group A versus Group B (see details in the joint Statistical Analysis Plan).

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

### 9.6. Exploratory Analyses

Analyses of the patient-reported outcome data collected in the duplicate phase 3 studies (MVT-601-3101 and MVT-601-3102) will be conducted to confirm the measurement properties of the NRS instruments used in the studies. These analyses include psychometric measurement properties focusing on test-retest reliability and construct validity. Details of these analyses will be provided in a separate Statistical Analysis Plan.

### 9.7. Interim Analyses

There are no planned interim efficacy analyses.

### 9.8. Study Committees and Communication

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

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

An independent Data 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. RESPONSIBILITIES

### 10.1. Investigator Responsibilities

#### 10.1.1. Good Clinical Practice

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

standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical study, the investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with the sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for 1 year following completion of the study.

### 10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

### 10.1.3. Informed Consent

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

### 10.1.4. Confidentiality

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

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

### 10.1.5. Study Files and Retention of Records

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

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

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

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

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

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

### 10.1.6. Electronic Case Report Forms

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

### 10.1.7. Investigational Product Accountability

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

At study initiation, the study monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with the sponsor requirements. Drug may be returned or destroyed once the study monitor has reviewed and returned used and unused study drug for accountability purposes. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor (or designee) for destruction or return of unused investigational medicinal product supplies.

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

### 10.1.8. Inspections

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

### 10.1.9. Protocol Compliance

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

## 10.2. Sponsor Responsibilities

### 10.2.1. Safety Reporting

The sponsor will comply with safety reporting requirements consistent with US FDA, EU National competent authority, and Health Canada Guidance 2.8.4, Health Canada Food and Drugs Act and Regulations, Division 5, Part C.05.014, and applicable ICH and regional regulatory safety reporting requirements.

### 10.2.2. Protocol Modifications

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

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

### 10.2.3. Study Report

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

### 10.2.4. Posting of Information on Publicly Available Clinical Trial Registers

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

## 10.3. Joint Investigator/Sponsor Responsibilities

### 10.3.1. Access to Information Monitoring

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

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

### 10.3.2. Access to Information for Auditing or Inspections

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

### 10.3.3. Study Discontinuation

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

### 10.3.4. Publications

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

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

No such communication, presentation, or publication will include Myovant Sciences GmbH confidential information (see Section 10.1).

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Myovant for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Myovant will detail the procedures for, and timing of, Myovant's review of publications.

# REFERENCES

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# APPENDICES

## Appendix 1. 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 2. Daily eDiary

Version 3 MY80005-eDiary
US English Screen Report 23May2017

# Screen report: my80005-eDiary Subject Facing

Localized texts are displayed in English.

## Contents

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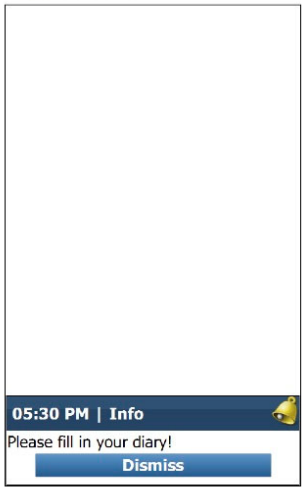
US English Screen Report

MY80005-eDiary
23May2017

## 1 Common




Message 1

Note: Time will populate per device

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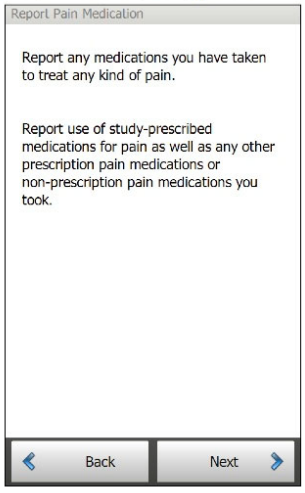
## 2 Form: MedReport

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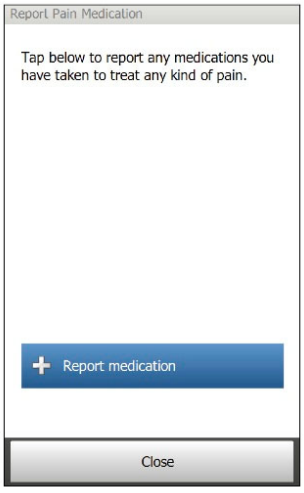


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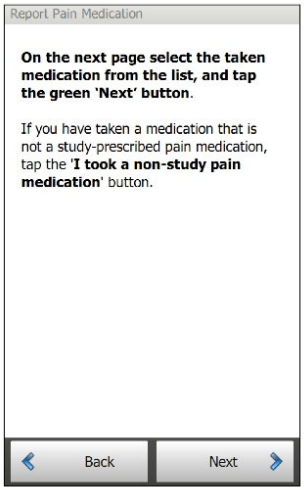


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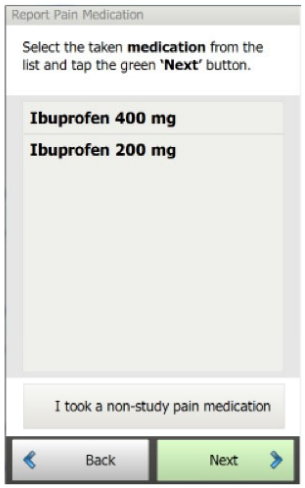


Screen 4

Note: Medications will show per patient set up


Message 1


Screen 5

Note: Medication and dates will update per Patient selection and per device

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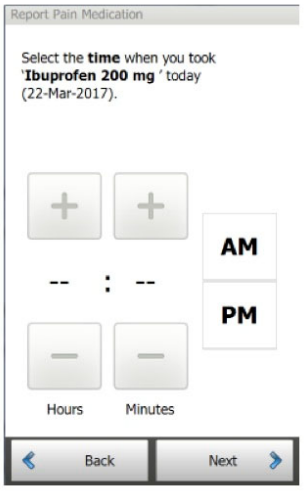
Message 2

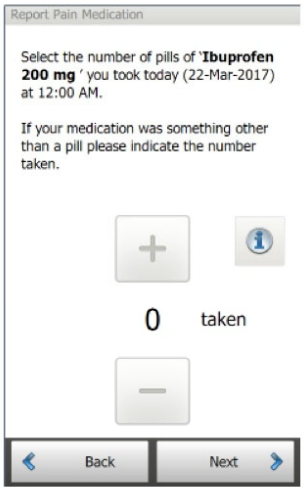



Screen 6


Message 3

Note: Medication Name and Date will show per device


Message 4

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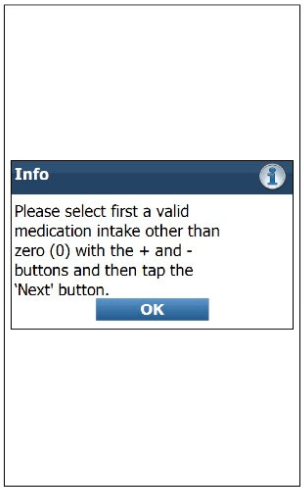


Message 5

Note: Medication Name and Date and time will show per device

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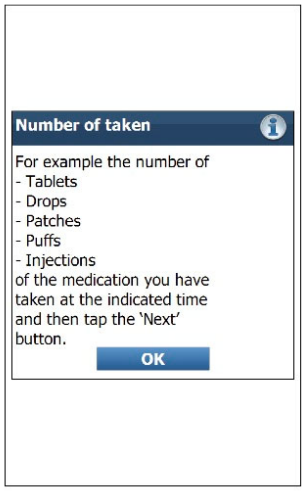


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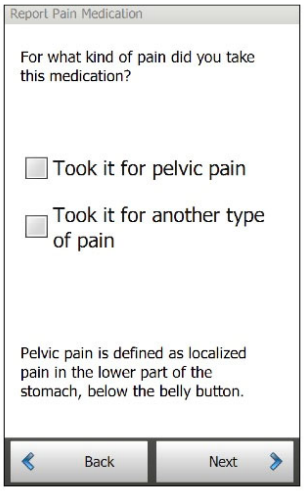


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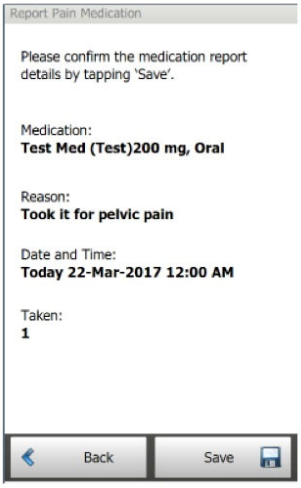
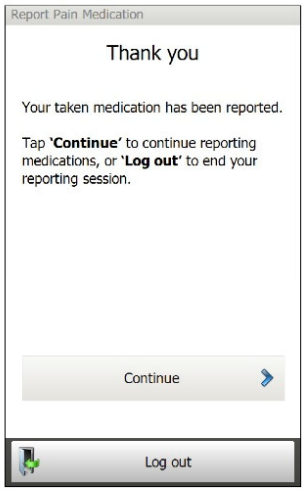



Screen 9

Note: 'Medication', 'Reason', 'Date and Time', 'Taken' will show per patient selection

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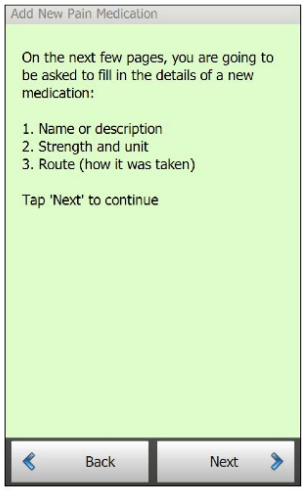


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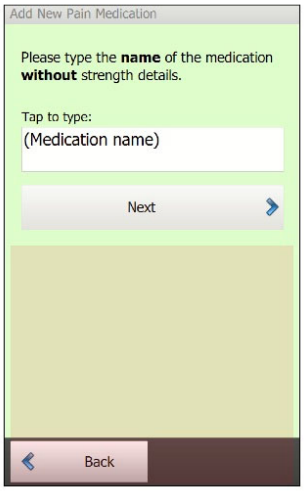


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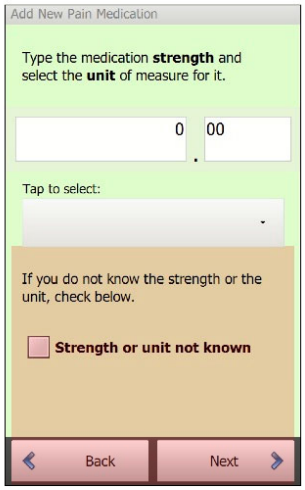
Message 7




Screen 13


Message 8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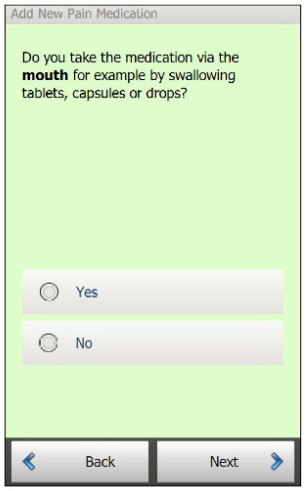


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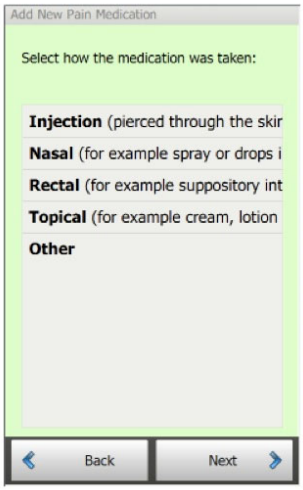


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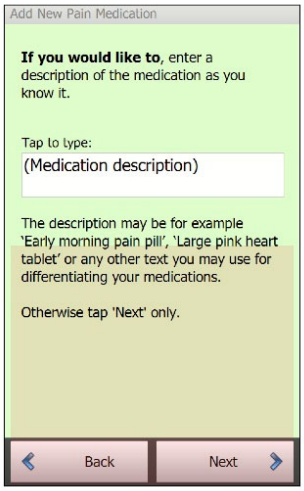


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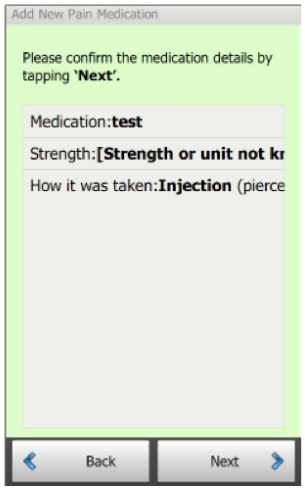


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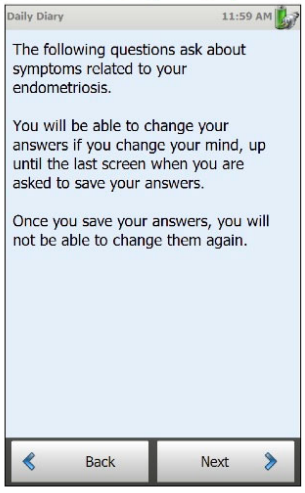
## 3 Form: Daily Diary

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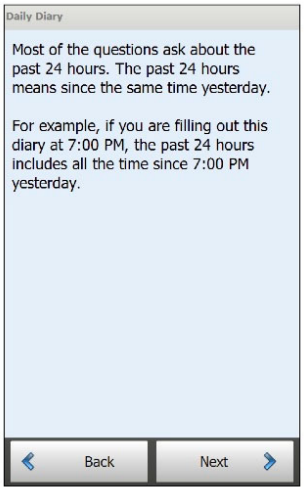


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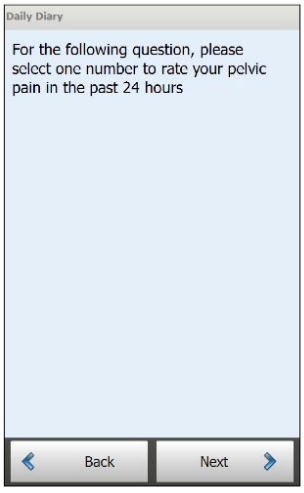


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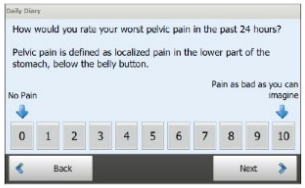


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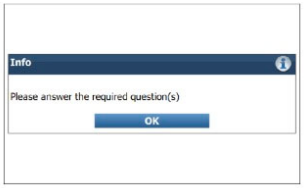


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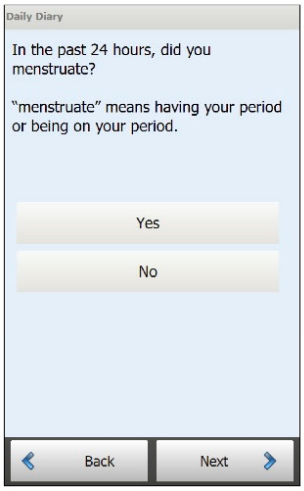


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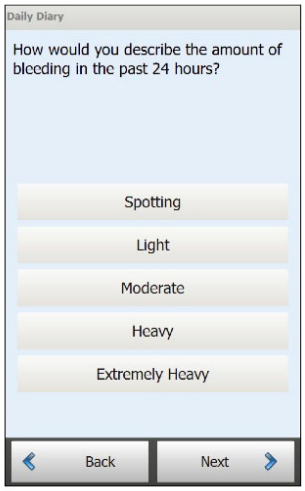


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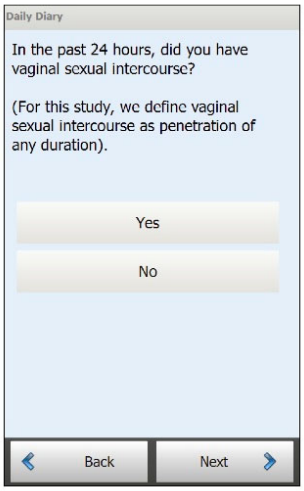


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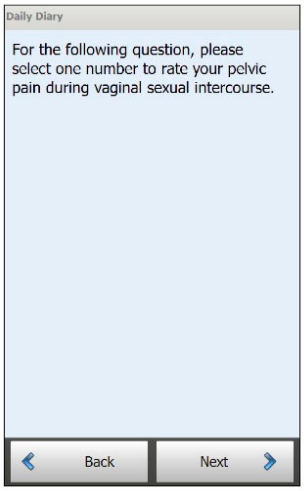


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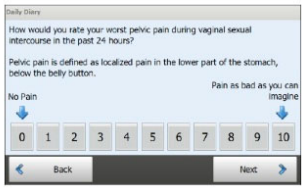


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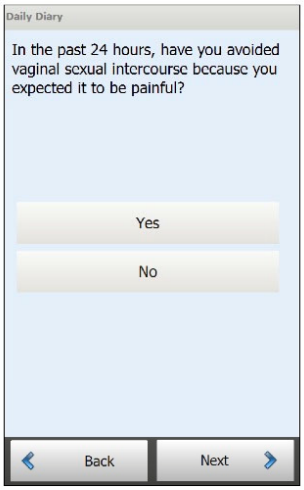


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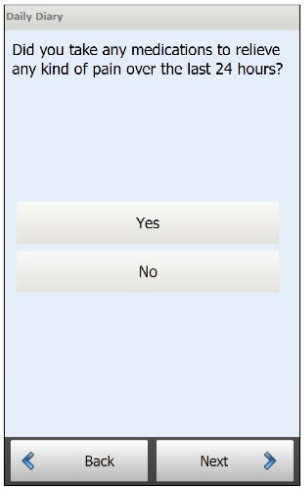


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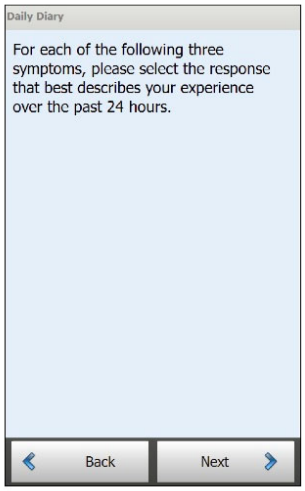


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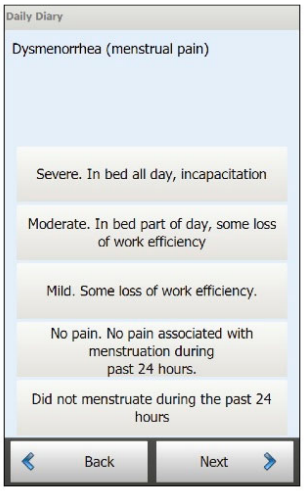


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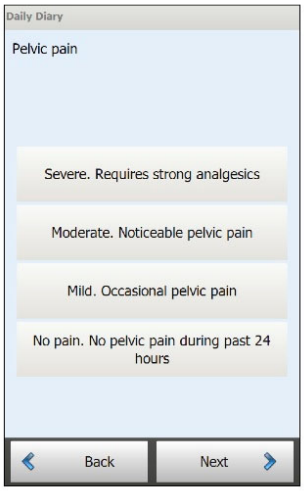


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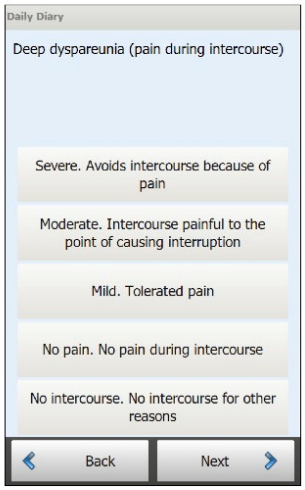
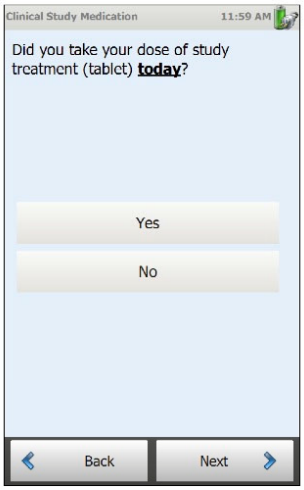
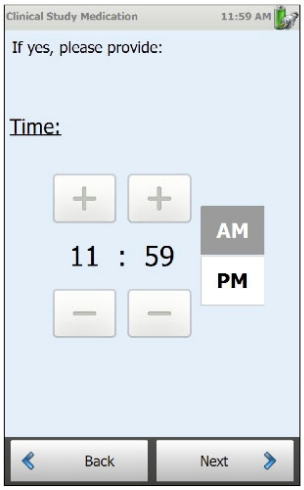



Screen 15




Screen 16




Screen 17

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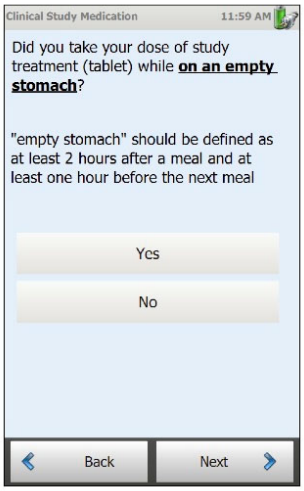
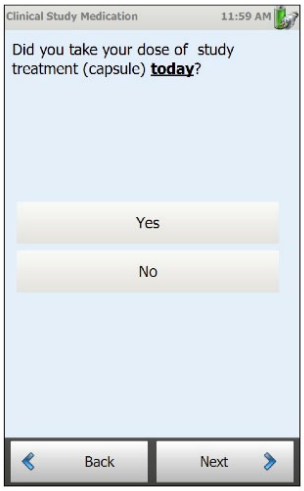
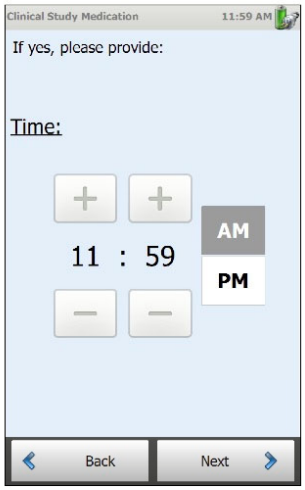
Message 2



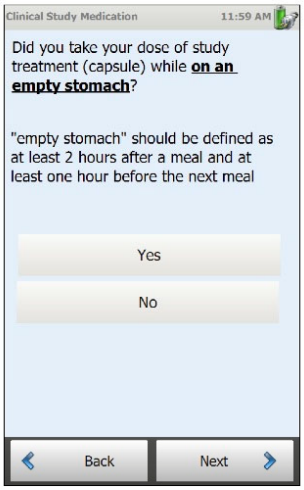

Screen 18



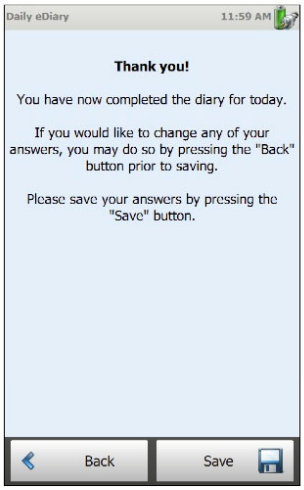

Screen 19




Screen 20




Screen 21




Screen 22

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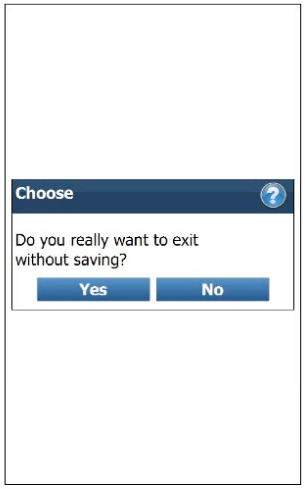


Message 1

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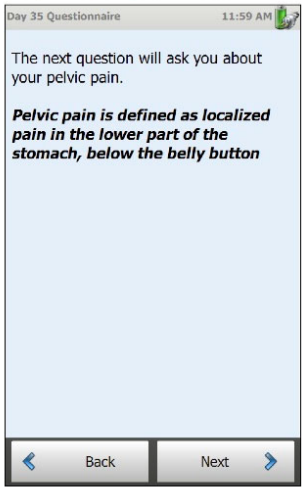
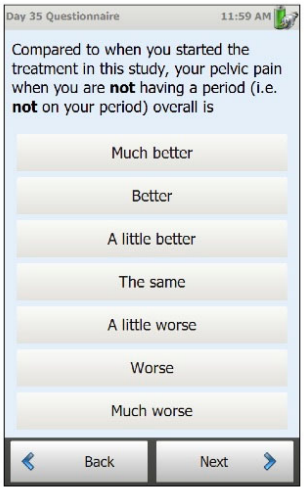
## 4 Form: PGIC-NMPP

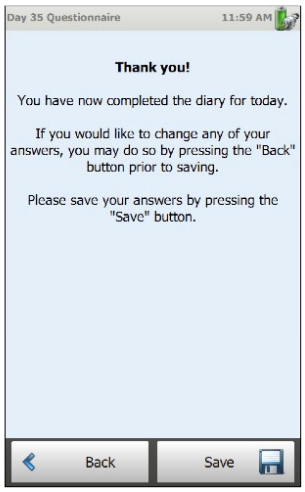



Screen 1




Screen 2


Message 1




Screen 3


Message 2

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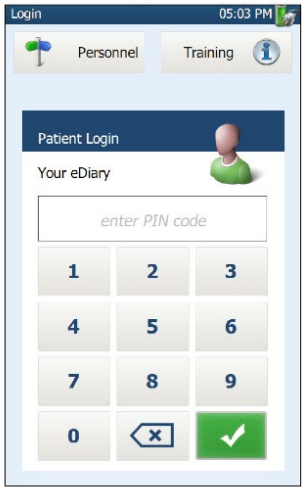
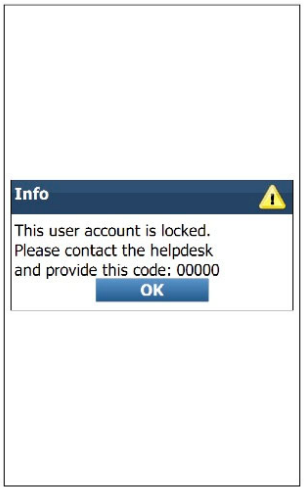
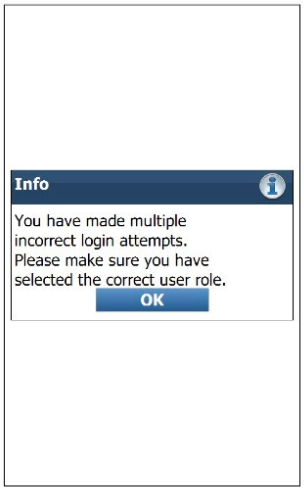
## 5 Form: Login




Screen 1




Message 1




Message 2


Message 3


Message 4


Message 5

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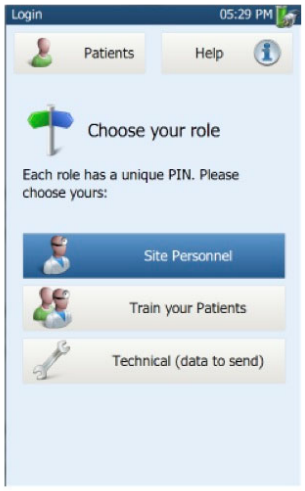
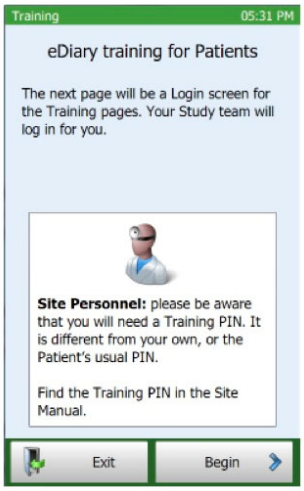
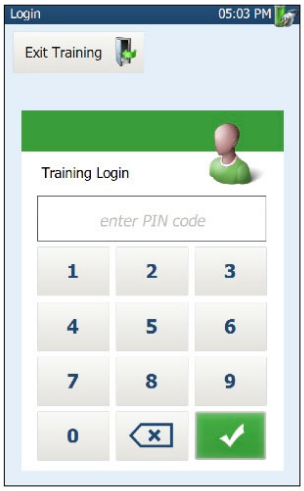


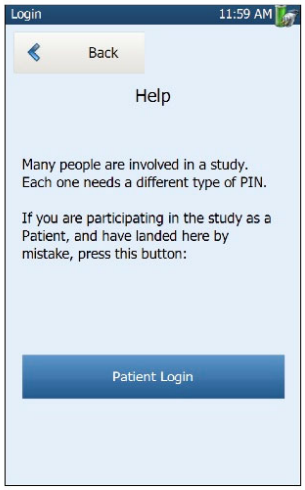

Screen 2




Screen 3




Screen 4




Screen 5


Screen 6

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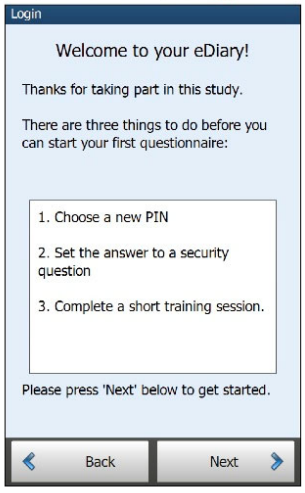
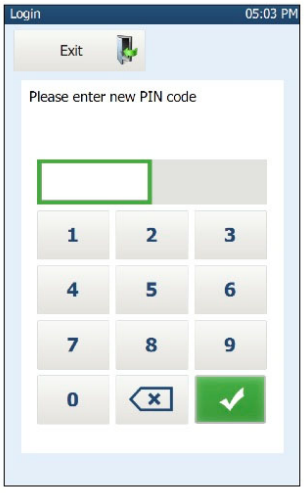
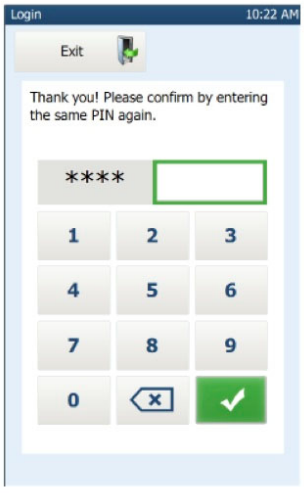
## 6 Form: PIN change




Screen 1




Screen 2




Screen 3


Message 1

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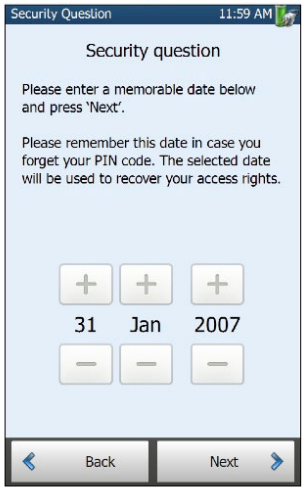
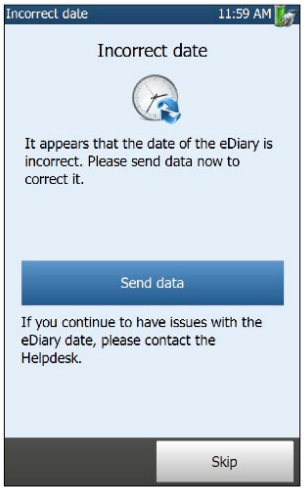
## 7 Form: Subject main menu

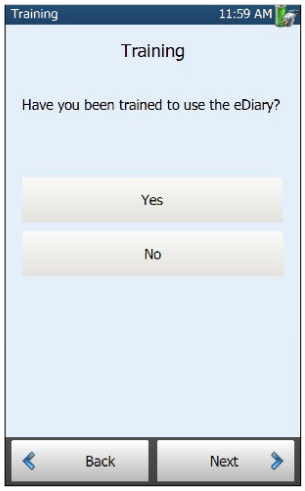



Screen 1

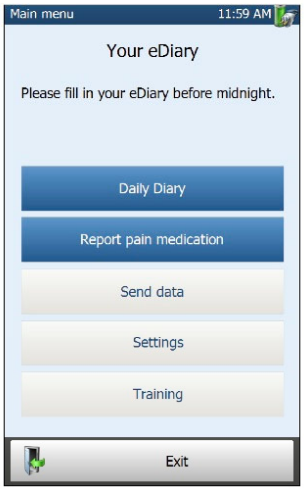

Message 1



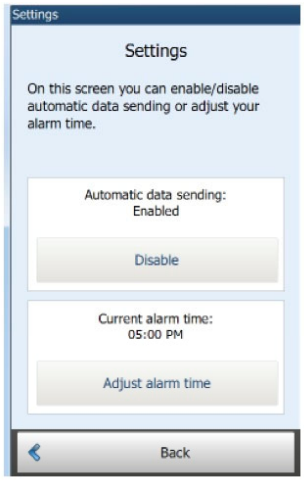

Screen 2




Screen 3




Screen 4




Screen 5

Note: Time will update per device

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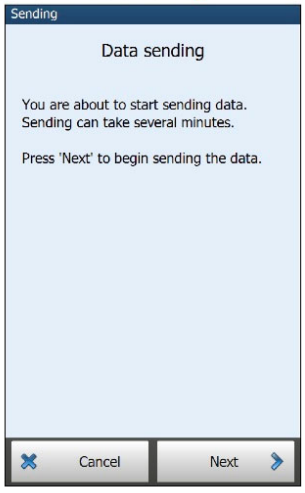
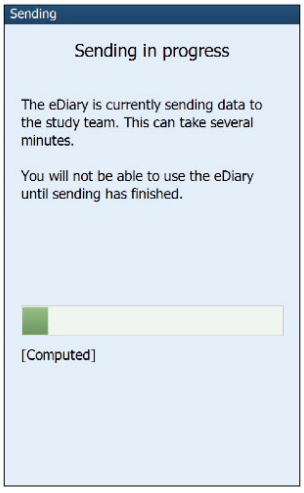
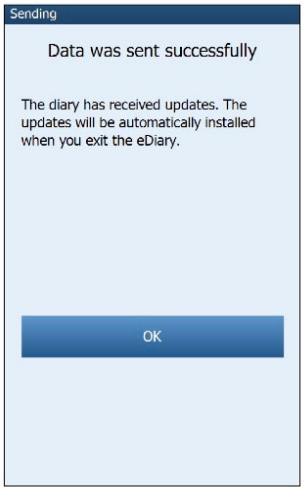
## 8 Form: Sending



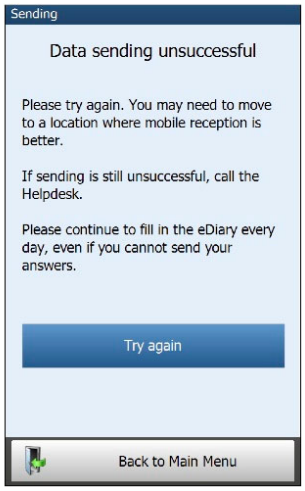

Screen 1



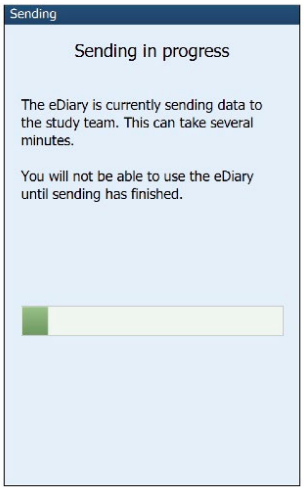

Screen 2




Screen 3




Screen 4




Screen 5

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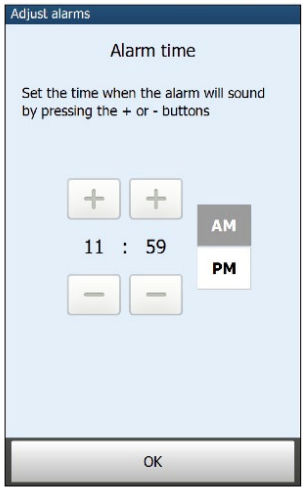
## 9 Form: AlarmSetup




Screen 1

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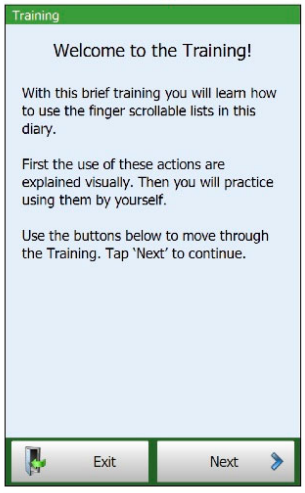
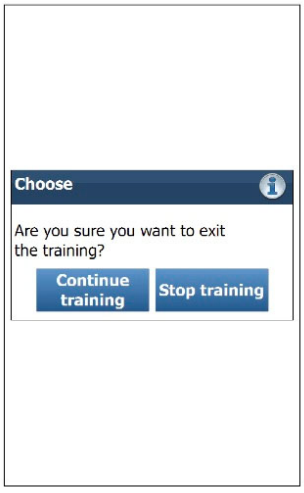
## 10 Form: Subject training diary

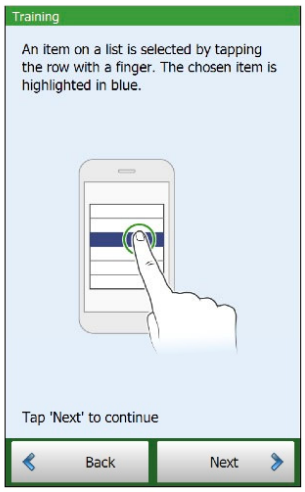



Screen 1


Message 1




Message 2




Screen 2


Screen 3


Message 3

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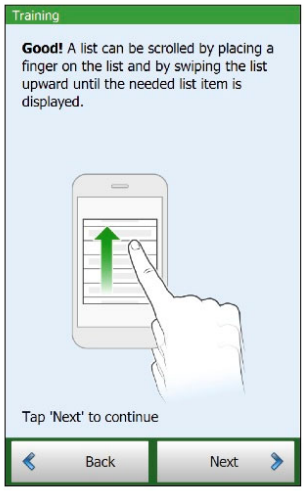
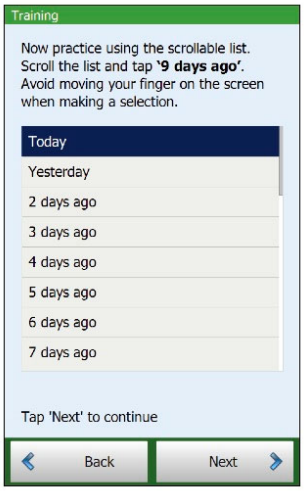
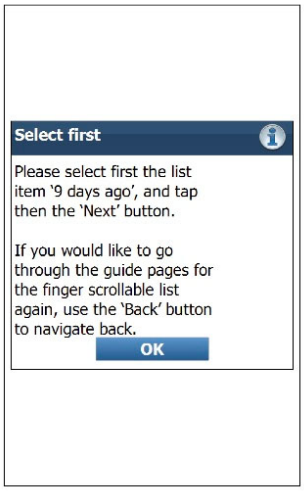


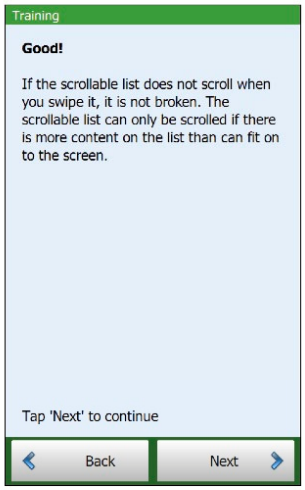

Screen 4



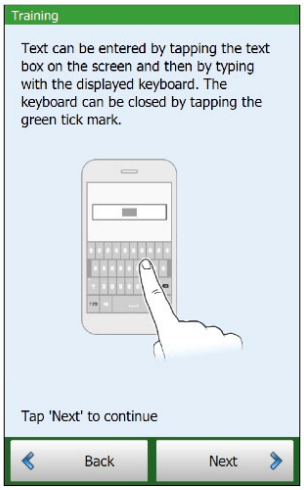

Screen 5



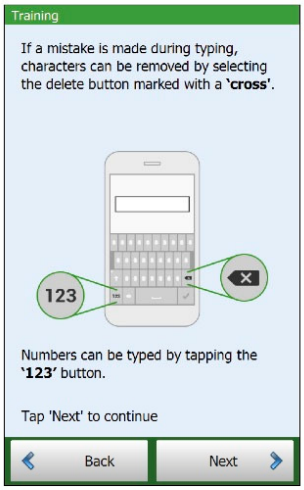

Message 4




Screen 6




Screen 7




Screen 8

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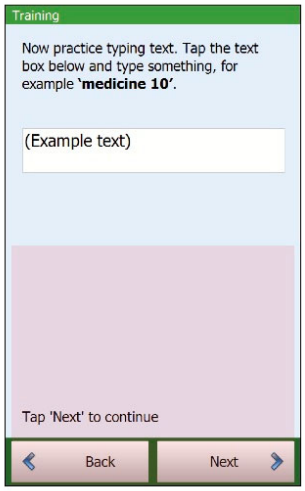
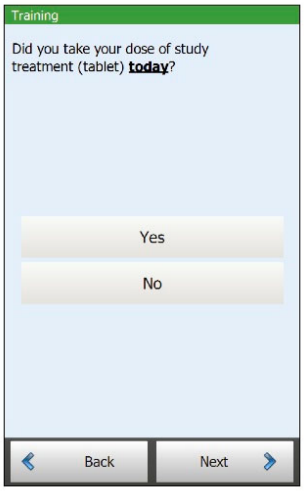
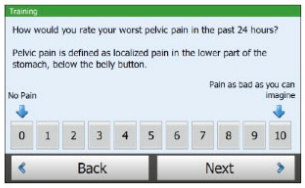



Screen 9



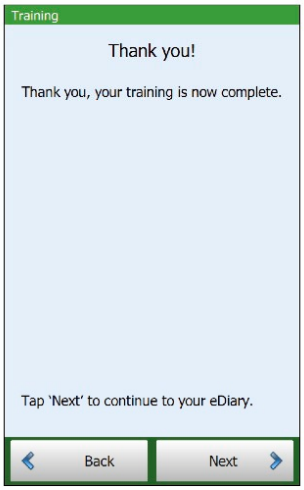

Screen 10


Message 5




Screen 11

Note: Screen will show latteraly on device

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## 11 Keyboards

## Appendix 3. Patient Global Impression of Change and Patient Global Assessments

### Patient Global Impression of Change (Dysmenorrhea)

Compared to when you started the treatment in this study, painful periods are

1. Much better
2. Better
3. A little better
4. The same
5. A little worse
6. Worse
7. Much worse

### Patient Global Impression of Change (Nonmenstrual Pelvic Pain)

Compared to when you started the treatment in this study, your pelvic pain when you are **not** having a period (i.e. **not** on your period) overall is

1. Much better
2. Better
3. A little better
4. The same
5. A little worse
6. Worse
7. Much worse

***Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button.***

### Patient Global Impression of Change (Dyspareunia)

Compared to when you started the treatment in this study, your pelvic pain when you have vaginal sexual intercourse is

1. Much better
2. Better
3. A little better
4. The same
5. A little worse
6. Worse
7. Much worse

☐ Not applicable: I have not had vaginal sexual intercourse since starting the study treatment

***For this study, we define vaginal sexual intercourse as penetration of any duration.***

**Patient Global Assessment (for pain)**

How would you rate your pelvic pain right now?

Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button

Absent
Mild
Moderate
Severe
Very Severe

**Patient Global Assessment (for dysmenorrhea during the past 4 weeks)**

In the past 4 weeks, did you have your period?

**If No:** Stop here.

**If Yes:** Continue to the question below.

In the past 4 weeks, how would you rate your pelvic pain on days you had your period (i.e., were on your period)?

Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button.

Absent

Mild

Moderate

Severe

Very Severe

**Patient Global Assessment (for nonmenstrual pelvic pain during the past 4 weeks)**

In the past 4 weeks, how would you rate your pelvic pain on days you did **not** have your period (i.e., were **not** on your period)?

Pelvic pain is defined as localized pain in the lower part of the stomach, below the belly button.

Absent
Mild
Moderate
Severe
Very Severe

**Patient Global Assessment (for function)**

How much were your daily activities limited by endometriosis over the last 4 weeks?

Not at all
Minimally
Moderately
Significantly
Very significantly

*Note: The PGA for dysmenorrhea, the PGA for nonmenstrual pelvic pain, and the PGA for function are administered via paper questionnaires.*

## Appendix 4. Endometriosis Health Profile - 30

ENDOMETRIOSIS HEALTH PROFILE QUESTIONNAIRE (EHP-30)

PART 1: CORE QUESTIONNAIRE

**DURING THE LAST 4 WEEKS,**
**BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...**

| | | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| **1.** | Been unable to go to social events because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **2.** | Been unable to do jobs around the house because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3.** | Found it difficult to stand because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **4.** | Found it difficult to sit because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **5.** | Found it difficult to walk because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **6.** | Found it difficult to exercise or do the leisure activities you would like to do because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |

Please verify that you have ***checked one box for each question***
before moving on to the next page.

**DURING THE LAST 4 WEEKS,**
**BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...**

| | | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| **7.** | Lost your appetite and/or been unable to eat because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **8.** | Been unable to sleep properly because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **9.** | Had to go to bed/lie down because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **10.** | Been unable to do the things you want because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **11.** | Felt unable to cope with the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **12.** | Generally felt unwell? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **13.** | Felt frustrated because your symptoms are not getting better? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **14.** | Felt frustrated because you are not able to control your symptoms? | ☐ | ☐ | ☐ | ☐ | ☐ |

Please verify that you have ***checked one box for each question***
before moving on to the next page.

**DURING THE LAST 4 WEEKS,**
**BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...**

| | | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| **15.** | Felt unable to forget your symptoms? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **16.** | Felt as though your symptoms are ruling your life? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **17.** | Felt your symptoms are taking away your life? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **18.** | Felt depressed? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **19.** | Felt weepy/tearful? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **20.** | Felt miserable? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **21.** | Had mood swings? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **22.** | Felt bad-tempered or short-tempered? | ☐ | ☐ | ☐ | ☐ | ☐ |

Please verify that you have ***checked one box for each question***
before moving on to the next page.

**DURING THE LAST 4 WEEKS,**
**BECAUSE OF YOUR ENDOMETRIOSIS, HOW OFTEN HAVE YOU...**

| | | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| **23.** | Felt violent or aggressive? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **24.** | Felt unable to tell others how you feel? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **25.** | Felt others do not understand what you are going through? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **26.** | Felt as though others think you are whining? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **27.** | Felt alone? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **28.** | Felt frustrated that you cannot always wear the clothes you would choose? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **29.** | Felt your appearance has been affected? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **30.** | Lacked confidence? | ☐ | ☐ | ☐ | ☐ | ☐ |

Please verify that you have ***checked one box for each question***.

# Appendix 5. Endometriosis Health Profile - Work Module

PART 2: MODULAR QUESTIONNAIRE

**Section A:**

These questions concern the effect endometriosis has had on your work **during the last 4 weeks**. If you have not been in paid or voluntary employment during the last 4 weeks please tick here ☐

**DURING THE LAST 4 WEEKS,**

**HOW OFTEN, BECAUSE OF YOUR ENDOMETRIOSIS, HAVE YOU...**

| | | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|---|
| 1. | Had to take time off work because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. | Been unable to carry out duties at work because of the pain? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. | Felt embarrassed about symptoms at work? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. | Felt guilty about taking time off work? | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. | Felt worried about not being able to do your job? | ☐ | ☐ | ☐ | ☐ | ☐ |

Please check that you have ***ticked one box for each question.***

MYOVANT_v1 02Jun2017



*Note: The EHP Work Domain is administered via a paper questionnaire.*

# Appendix 6. European Quality of Life Five-Dimension Five-Level Scale

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

**MOBILITY**

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

**SELF-CARE**

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

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

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

**PAIN / DISCOMFORT**

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

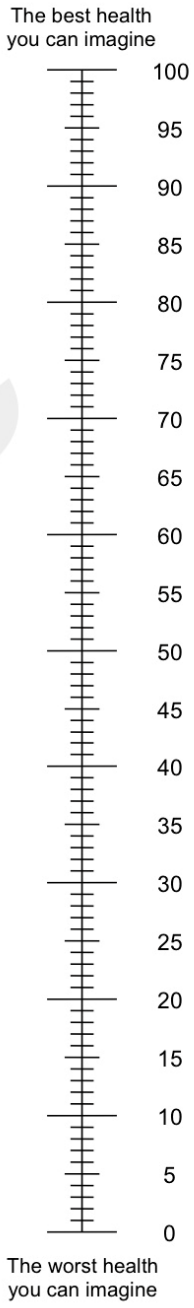
**ANXIETY / DEPRESSION**

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

2

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

YOUR HEALTH TODAY = ☐



## Appendix 7. Assessment of Abnormal Liver Function Tests

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

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

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

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

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

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

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

**Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests**

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

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

## Appendix 8. Protocol-Specified Rescue Analgesics

The medications below are listed based on their dose strength. The prescription (or instructions for use) for these medications may allow for use of more than one tablet at any given time. Analgesics should be prescribed in accordance with the respective country's approved product labeling. The subject's historical use of opioid analgesics should be taken into consideration when prescribing these drugs.

**Only one** Tier 2 medication should be selected for a given patient to be used throughout the study.

Study-specified analgesics include:

- Tier 1
  - ibuprofen (200 mg dose strength)[1]

- Tier 2
  - tramadol (37.5 mg) / paracetamol (325 mg)
  - tramadol (50 mg)
  - codeine (30 mg)
  - codeine (30 mg) / paracetamol (300 mg)
  - codeine (30 mg) / paracetamol (500 mg)
  - codeine 15 mg/ paracetamol (500 mg)
  - hydrocodone (5 mg) / acetaminophen 325 mg

Please consult your site-specific instructions for study-specified analgesics for your country.

[1]All second-tier drugs that contain acetaminophen or paracetamol are fixed-dose combination products (eg, single tablet containing both drugs).