16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Protocol Original

Protocol Amendment 1

Protocol Amendment 1 Summary of Changes

Protocol Amendment 2

Protocol Amendment 2 Summary of Changes

Protocol Amendment 3

Protocol Amendment 3 Summary of Changes

Protocol Amendment 3.1

Protocol Amendment 3.1 Summary of Changes

CLINICAL STUDY PROTOCOL

Study Title:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifiers:	IND# 076642 EudraCT # 2017-004066-10
Version and Effective Date:	Original: 25-OCT-2017 06-NOV-2017

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SPONSOR SIGNATURE PAGE

SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain

Protocol Number: MVT-601-3103

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

PPD

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Date

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Date

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06-Nov-2017

Date

PPD

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06 NOV 2017

Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dihyroepiandrosterone
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
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
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NMPP	nonmenstrual pelvic pain
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PLD	phospholipidosis
QTc	corrected QT (interval)
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
sB&B	Subject Modified Biberoglu and Behrman
ULN	upper limit of normal
US	United States
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Protocol Number	MVT-601-3103
Location	Multinational, including North and South America, Europe, Africa, New Zealand, and Australia
Study Centers	Approximately 320 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with endometriosis-associated pain
Number of Patients Planned	Approximately 800
Study Objectives	In women with endometriosis-associated pain, the study objectives are as follows: <u>Primary Efficacy Objective</u> • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.

	Secondary Efficacy Objectives • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: o Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; o Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea; o Patient Global Impression of Change (PGIC) for dysmenorrhea; o Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; o PGIC for NMPP; o Dyspareunia, measured by the NRS; o PGIC for dyspareunia; o Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]); o Patient Global Assessment (PGA) for pain; o PGA for function; o Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains; o Dysmenorrhea-related functional effects (sB&B); o NMPP-related functional effects (sB&B). Safety Objectives • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: o Adverse events; o Changes in bone mineral density. Pharmacodynamic Objective • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.

	Exploratory Objective • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).

Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 28 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study, and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit, and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks.

During the 28-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the electronic diary (eDiary). Only study-specific rescue analgesic medications will be allowed starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).

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

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

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

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

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.
3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic

abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study.

1. Has had gynecological surgery or other surgical procedures for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.9.1;
6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.

12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor; 13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).	
Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 28 weeks (Open-Label Treatment Period). Concomitant Medicinal Products Systematically Prescribed for All Study Patients Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug 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. The analgesics for each patient will be the same as those prescribed for her during the parent study.
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study. Primary Efficacy Endpoints • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores.

	Secondary Efficacy Endpoints • Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores; • Change from the parent study Baseline to Week 52/end of treatment (EOT) in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 52/EOT; • Change from the parent study Baseline to Week 52/EOT in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP at Week 52/EOT; • Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 52/EOT; • Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline to Week 52/EOT in severity scores on the PGA for pain; • Change from the parent study Baseline to Week 52/EOT in function impairment on the PGA for function; • Change from the parent study Baseline to Week 52/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period to Week 52/EOT in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period to Week 52/EOT in NMPP-related functional effects (sB&B). Safety Endpoints • Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. Pharmacodynamic Endpoint • Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol. Exploratory Endpoints • Change from Baseline to Week 52/EOT in the EHP-30 scale total score; • Change from Baseline to Week 52/EOT in the EHP Work Domain score; • Change from parent study Baseline to Week 52/EOT in the EQ-5D-5L.

Statistical Methods

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

Efficacy

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

The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

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

Safety

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

Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, high level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values will be classified by toxicity grade based on the National Cancer Institute CTCAE. Laboratory shift tables of the parent study Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits. The absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change at Week 52 from parent study Baseline in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3101 or MVT-601-3102) and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3103

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Informed Consent	X[d]									
Review Eligibility Criteria	X									
Concomitant Medications[e]	X[f]	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X[g]	X	X	X	X	X	X	X	X[h]	X
Weight	X[g]			X				X	X[h]	
Complete Physical Exam	X[g]							X	X[h]	
Visual Acuity[i]	X[g]									
Signs and Symptoms-Directed Physical Exam[j]		X	X	X	X	X	X		X[h]	X
12-Lead ECG[k]	X[g]							X	X[h]	
Clinical Laboratory Tests[l]	X[g,m]	X	X	X	X	X	X	X[m]	X[h]	X
Pharmacodynamics Sample[n]	X[g,m]							X[m]	X[h,m]	
Urinalysis	X[g]							X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X[h]	X

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Daily eDiary[o]	X[g]	X	X	X	X	X	X	X		X
Site Review of eDiary Data	X[g]	X	X	X	X	X	X	X	X[h]	X
Bone Densitometry[p]	X[g]			X				X[q,r]	X[h]	
Endometrial Biopsy	X[g,s]								X[h]	
Dispense Study Treatment	X	X	X	X	X	X	X		X[h]	
Dispense or prescribe protocol-specified analgesic drugs[t]	X	X	X	X	X	X	X	X	X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic	X[u]							X	X[h]	
Daily Self-Administration of Study Treatment[v]		X								
Take Protocol-specified Rescue Analgesics as Needed[w]	X									
EHP-30 Questionnaire[x]	X[g]			X			X	X	X[h]	
Patient Global Assessment for Pain[x]	X[g]	X	X	X	X	X	X	X	X[h]	
Patient Global Assessment for Function[y]	X[g]	X	X	X	X	X	X	X	X[h]	
Patient Global Impression of Change[x]	X[g]			X				X	X[h]	

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
EHP Work Domain[y]	X[g]							X	X[h]	
EQ-5D-5L Questionnaire[x]	X[g]							X	X[h]	
Adverse Event Collection[z]	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery										X[aa]

Abbreviations: BP, blood pressure; DXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; eDiary, electronic diary; EHP, Endometriosis Health Profile; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; exam, examination; HR, heart rate; NRS, Numerical Rating Scale; sB&B, Subject Modified Biberoglu and Behrman.

a. The Week 52 visit should occur on or after the 1-year anniversary of Study Day 1 of the parent study.
b. Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.
c. The Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit.
d. May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3103 is defined by administration of the first dose of MVT-601-3103 study drug.
e. Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up Period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3103 should be reported as concomitant medications in the parent study (MVT-601-3101 or MVT-601-3102). If concomitant medication is ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.
f. Concomitant medications are recorded both for the parent study and for MVT-601-3103 at the Week 24/Baseline visit. (See footnote e for further details).
g. This is a parent study (MVT-601-3101 or MVT-601-3102) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3103 and is covered under the informed consent for the parent study.
h. The indicated procedure may be performed at the Unscheduled visit based on the purpose of the visit (eg, follow-up for an adverse event or abnormal laboratory test).
i. See parent study protocols (MVT-601-3101 or MVT-601-3102) for instructions on testing visual acuity.
j. The exam may include a gynecologic examination, if indicated based on signs and symptoms.
k. The 12-lead ECGs will be submitted for central reading.
l. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, and Week 52. At the Week 24/Baseline visit and Week 52 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.
m. Samples should be obtained in a fasted state (at least 8 hours). Water is allowed during the fasting period.

n. For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week 52/Early Termination, collect samples for analysis of estradiol concentrations only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are completed.
o. At the Week 24/Baseline visit, transition the patient within her eDiary from the parent study to MVT-601-3103. The eDiary data collection will include NRS pain scores, menstruation information (including severity of bleeding), analgesic drug use, date and time of study drug administration, and sB&B scale scores.
p. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading.
q. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.
r. Patients with a bone mineral density loss of > 3% at their Week 52/Early Termination visit relative to parent study Baseline measurement will undergo a follow-up bone densitometry scan at 6 (±1) months and will be contacted to question them about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.
s. Endometrial biopsies are to be done per instructions in the parent study. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details).
t. Please see Appendix 1 for list of protocol-specified analgesics and see the Study Reference Manual for information on where and how to obtain protocol-specified analgesic medications by country. At the Week 52 visit, patients who will not be proceeding to another 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 another extension study, refer to the protocol for that next study.
u. Pregnancy test must be negative before the study drug dose is administered.
v. Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week 52/Early Termination visit.
w. Patients may only take their study-specified analgesics for pain. Analgesics should **not** be taken prophylactically (ie, in anticipation of pain).
x. The patient will enter her response(s) into an electronic tablet device at the site.
y. The patient will enter her response onto a paper questionnaire at the site.
z. Collect adverse events from the time that the first dose of study drug for MVT-601-3103 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3103 should be reported as an adverse event in the parent study (MVT-601-3101 or MVT-601-3102). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.
aa. Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted again by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.

2. INTRODUCTION

2.1. 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 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

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

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once-daily oral medication for the treatment of 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 was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

3. STUDY OBJECTIVES AND ENDPOINTS

Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) for the following parent study treatment groups:

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

The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study.

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

Objectives	Endpoints
Primary Efficacy	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	• Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores.
Secondary Efficacy	
To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following:	
• Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain;	• Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores;
• Dysmenorrhea, as measured by the NRS for dysmenorrhea;	• Change from the parent study Baseline to Week 52/end of treatment (EOT) in the mean dysmenorrhea NRS score;
• Patient Global Impression of Change (PGIC) for dysmenorrhea;	• Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 52/EOT;
• NMPP, as measured by the NRS for NMPP;	• Change from the parent study Baseline to Week 52/EOT in the mean NMPP NRS score;
• PGIC for NMPP;	• Proportion of patients who are better or much better on the PGIC for NMPP at Week 52/EOT;
• Dyspareunia, measured by the NRS;	• Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia NRS scores;
• PGIC for dyspareunia;	• Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 52/EOT;
• Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]);	• Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia functional impairment on the sB&B scale;
• Patient Global Assessment (PGA) for pain;	• Change from the parent study Baseline to Week 52/EOT in severity scores on the PGA for pain;

Objectives	Endpoints
• PGA for function;	• Change from the parent study Baseline to Week 52/EOT in function impairment on the PGA for function;
• Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains;	• Change from the parent study Baseline to Week 52/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
• Dysmenorrhea-related functional effects (sB&B);	• Change from the parent study Baseline pain assessment period to Week 52/EOT in dysmenorrhea-related functional effects (sB&B);
• NMPP-related functional effects (sB&B).	• Change from the parent study Baseline pain assessment period to Week 52/EOT in NMPP-related functional effects (sB&B).
Safety	
To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	
• Adverse events;	• Incidence of adverse events;
• Changes in bone mineral density.	• Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	• Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol.

Objectives	Endpoints
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52-weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	• Change from Baseline to Week 52/EOT in the EHP-30 scale total score; • Change from Baseline to Week 52/EOT in the EHP Work Domain score; • Change from parent study Baseline to Week 52/EOT in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 28 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study, and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit, and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study

drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks.

During the 28-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the electronic diary (eDiary). Only study-specific rescue analgesic medications will be allowed starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via DXA.

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

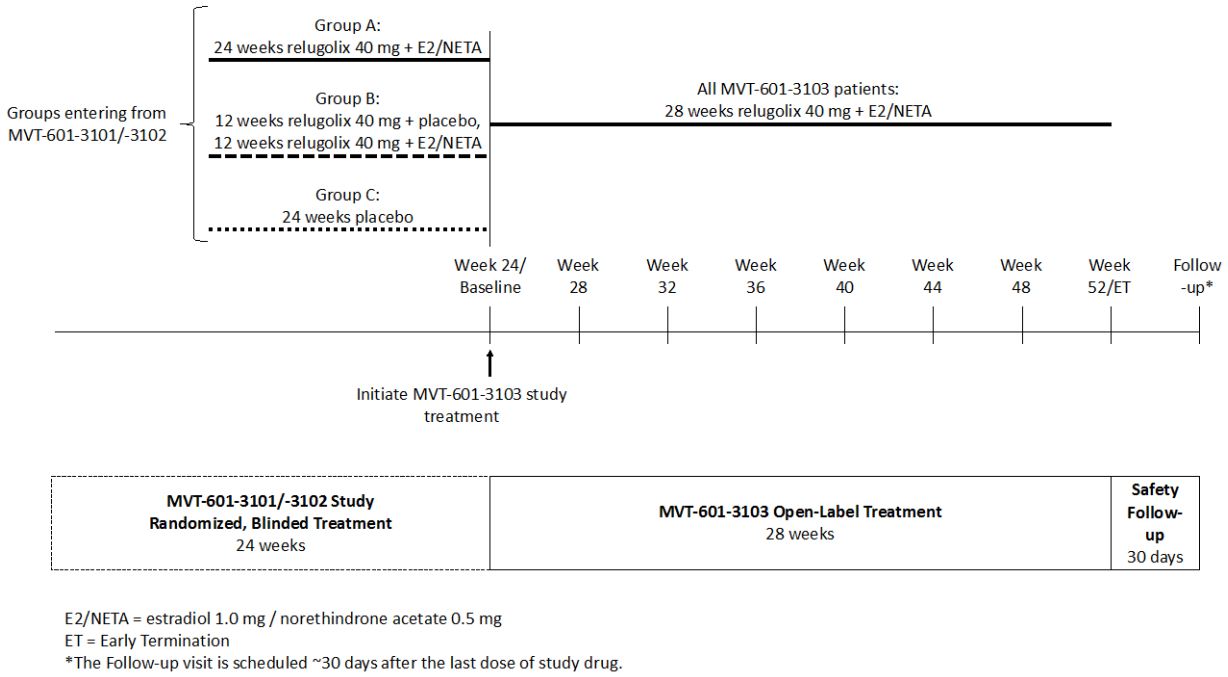
Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months after the last dose of study medication.

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

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

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

Figure 4-1 MVT-601-3103 Study Schematic



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

4.2. Discussion of Study Design, Including Dosing

The SPIRIT EXTENSION study (MVT-601-3103) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3101 and MVT-601-3102) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with endometriosis-associated pain. This 28-week extension study provides additional efficacy and safety data up to 52 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids

demonstrated the 40-mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 52 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 52 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2017; Lee, 2016; Franke, 2000] or endometriosis-associated pain [Wu, 2014]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the United States (US) as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol

concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3101 and MVT-601-3102) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a significant decrease in endometriosis-associated pain in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose estradiol and norethindrone acetate to decrease dysmenorrhea and NMPP and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 28 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102). This study design will allow eligible patients with endometriosis-associated pain, who were randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 800 premenopausal women aged 18 to 51 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. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.

3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria

1. Has had gynecological surgery or other surgical procedures for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.9.1;

6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.
12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor;
13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).

4.4. Method of Assigning Patients to Treatment Group and Patient Identification Number

Eligible patients who sign consent will be identified with the same Patient Identification (ID) Number assigned to the patient during the parent study. This extension study is a single-arm

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

4.5. Removal of Patients from Therapy

Completion of the Week 52 visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 52 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).

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

- Any adverse event that is intolerable to the patient and that cannot be ameliorated by the use of adequate medical intervention, or that in the opinion of the investigator or medical monitor would lead to undue risk to the patient if dosing continued;
- If it is discovered after enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. 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 of eDiary completion. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

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

4.6. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use nonhormonal contraception throughout the study unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™) at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Has a nonhormonal intrauterine device (eg, Paragard®) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as described below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

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

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

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

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

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

pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

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

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

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

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

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

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 1.

5.2. Identity of Investigational Product

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

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

5.2.1. Product Characteristics

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

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

5.3. Randomization and Stratification

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

5.4. Directions for Administration

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

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

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

5.5. Dose Reduction/Dose Administration

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

5.6. Storage, Packaging, and Labeling

Study drug should be stored in an appropriate, limited-access, secure location within a temperature range of 20°C to 25°C with excursion to 15°C to 30°C permitted until it is used or returned to the sponsor (or designee). Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual and Pharmacy 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 and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the Study Reference Manual.

5.7. Blinding

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

5.8. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and should bring all unused and used study drug to each study visit.

Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Because of the importance to both safety and efficacy evaluation, patients who are grossly noncompliant with eDiary completion must undergo an Unscheduled visit to evaluate reasons for noncompliance 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 4.5 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.

5.9. Prior and Concomitant Medications and Non-Drug Therapies

5.9.1. Prohibited Medications

Table 5-2 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 5-2 are prohibited at any time during the study through the Follow-Up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-2 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	

Drug Class	Examples	Comments
GnRH analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-androgens	danazol	
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	Note: All other anticonvulsants are allowed
Aromatase inhibitors	anastrozole letrozole	
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective estrogen receptor modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective progesterone receptor modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine devices	levonorgestrel copper	
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.

Drug Class	Examples	Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir[f]	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.
Moderate and strong P-glycoprotein inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Drug Class	Examples	Comments
Analgesic drugs **other** than those specified for use during the study	Acetaminophen/paracetamol (other than any included in a study-specified analgesic) aspirin > 325 mg/day NSAIDs (other than study-specified NSAIDs) gabapentin pregabalin carbamazepine metamizole	Note: Aspirin ≤ 325 mg per day is allowed
Antidepressants New treatment or changed doses of SSRI, SNRI, or TCA antidepressants	**SNRI examples:** duloxetine venlafaxine desvenlafaxine **SSRI examples:** citalopram fluoxetine paroxetine fluvoxamine **TCA examples:** amitriptyline doxepin desipramine nortriptyline	SSRI, SNRI, or TCA allowed if given at the same dose as used during the 3 months prior to the Run-In Period of MVT-601-3101 or MVT-601-3102. 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.

Abbreviation: GnRH, gonadotropin-releasing hormone; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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

5.9.2. Permitted Medications

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

5.9.2.1. Analgesics

All analgesics will be collected in the eDiary and recorded in the electronic Case Report Forms (eCRFs).

5.9.3. Prohibited Non-Drug Therapies

Surgical treatment of endometriosis is prohibited from the Week 24/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 2 periods: Open-Label Treatment Period and Safety Follow-Up Period. Unscheduled visits may occur as needed to evaluate patients.

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

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3101 or MVT-601-3102 will serve as the Week 24/Baseline procedures for patients who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

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

- Informed consent (unless signed previously);
- Record concomitant medications;
- Dispense study treatment;
- Dispense or prescribe protocol-specified analgesic drugs;
- Transition the patient within her eDiary from the parent study to MVT-601-3103
- Take study drug dose in clinic; and
- Record adverse events, if any.

The Week 24 visit date in the parent study is defined as the date that the last procedures for the Week 24 visit were completed, acknowledging that the Week 24 visit procedures may be completed on different dates. Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit, and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit.

Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, and 52.

Accountability for study drug will be performed at each visit. Instructions for analgesic medication usage will be reinforced at each visit.

Questionnaires are administered on the electronic tablet and on paper at each visit. These procedures should occur before any other types of study procedures are performed.

Patients will bring their eDiary, analgesic medications, and study drug to each visit. The site must document the start and stop dates of the patient's menses.

An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details). Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, and Week 52. At the Week 24/Baseline visit and Week 52 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.

ECGs will be done at the Week 24/Baseline and at the Week 52/Early Termination visits. Bone densitometry will occur at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits. Week 52/Early Termination. Bone densitometry and ECGs will be submitted for central reading.

Study drug compliance will be reviewed at each visit. Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

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

6.3. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 52 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 52; however, for patients whose last dose of study drug is during Week 32 or earlier, the bone densitometry 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(s).

Patients (including those who complete the Week 52 visit and those who withdraw early from this study) will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week 52 visit, the Follow-up visit may be waived.

The Follow-up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.4. Unscheduled Visits

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

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Pharmacodynamics Sample Collection

A blood sample for the pharmacodynamic analysis of serum estradiol will be collected pre-dose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week 52 or the Early Termination visit, when no dose is administered. These pharmacodynamic samples will be analyzed at a central laboratory. These results will not be shared with the sites at any time.

6.5.1.2. Patient eDiary

All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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.

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

6.5.1.3. 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 3). Patients will complete the EHP-30 questionnaire at the site at visits indicated in Section 1.1 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.

6.5.1.4. 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 4). 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 visits indicated in Section 1.1 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.

6.5.1.5. 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 5) 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. The PGA for pain severity and the PGIC will be completed on a tablet device at the study site. The PGA for function will be completed on a paper questionnaire at the study site.

6.5.1.6. 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 6). Patients will complete the EHP Work Domain questionnaire at visits indicated in Section 1.1 before other types of study procedures, such as blood draws and physical examinations, are performed. The EHP Work Domain will be completed on a paper questionnaire at the study site.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

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

6.5.2.2. Vital Signs

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

6.5.2.3. Physical Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment.

6.5.2.4. 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
Creatine kinase		Urine Microscopy (reflex testing based on abnormal urine analysis)
Hemoglobin A1c		
Bilirubin total		
Alanine aminotransferase		
Aspartate aminotransferase		
Gamma-glutamyl transferase		
Alkaline phosphatase		

Hormones	Lipids	Pregnancy
Estradiol	Total cholesterol Low density lipoprotein High density lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, 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.

6.5.2.5. 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 the central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient) at the time points described in the Schedule of Activities (Section 1.1). The scans will be read by the central imaging laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient and should be the same as used for the patient during the parent study (MVT-601-3101 and MVT-601-3102). The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study.

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

about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.

Patients who experience a bone mineral density loss from the parent study Baseline of ≥ 7% at any of the anatomical sites assessed will be discontinued from the extension study and will undergo another bone densitometry scan as described above. Patients should be assessed for secondary causes of bone loss and followed up further if not improving on the 6-month follow-up scan, unless an alternative etiology has been identified.

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

6.5.2.7. Status of Menstruation Recovery

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

7. SAFETY CONSIDERATIONS

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

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 and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

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

7.3. Assigning Causal Relationship to Study Drug

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

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

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

7.4. Assigning Severity Rating for Adverse Events

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

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

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

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

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

7.5. Adverse Events of Clinical Interest Reporting

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

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

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

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

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

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the 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 QuintilesIMS Safety & Risk Management:

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-601-3103);
- Site address and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity);
- Causal relationship to the study drug.

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

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

7.7. Study Drug Overdose Management

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

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

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

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

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for pharmacokinetic analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy 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 form, as available.

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

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

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on 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

(corrected QT [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD), reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

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

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the parent studies.	Bone mineral density will be monitored at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the parent studies.	12-lead ECG at the Week 24/Baseline and Week 52/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal liver test results (AST or ALT > 3 x ULN) that develop during the Open-Label Treatment Period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with phospholipidosis (PLD). PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 24/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

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

8.2. Monitoring

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

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

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced (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 (SAP) will describe the detailed statistical methods and analyses for this study.

All efficacy and safety measures over the course of both the parent and extension studies will be presented by the parent study treatment group using descriptive statistics. No formal treatment comparisons will be performed for this extension study. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

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

9.2. Analysis Populations

Efficacy data analyses will be performed on the Intent-to-Treat (ITT) Population, defined as all patients who were randomized in a parent study (MVT-601-3101 or MVT-601-3102) and who have received any amount of randomized study drug.

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

The analysis methods for safety and efficacy endpoints are the same as those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Justification

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

9.4. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the ITT Population.

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

The point estimates and 2-sided 95% confidence intervals (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline. Patients who had a pain reduction less than the pre-determined threshold or who had an increase in the use of analgesics for endometriosis-associated pain will be considered non-responders. The pain reduction thresholds will be determined for NMPP and dysmenorrhea separately (see the SAP for details) for the parent studies and these same thresholds will be applied to this study.

Baseline values are calculated using the Baseline pain assessment period, which is defined as the period from the date of the first dose of placebo in the parent study Run-In Period through the day prior to the date of randomization. Patients' average NRS pain scores and use of rescue analgesic medications for endometriosis-associated pain (dysmenorrhea or NMPP) will be compared between a given visit-specific pain assessment period (eg, Week 28, Week 32, etc.) and the Baseline pain assessment period. The visit-specific pain assessment period is defined as the last 35 calendar days immediately prior to and including the last dose of study drug treatment received prior to the visit date.

For any pain assessment period (Baseline or visit-specific), the average NRS scores will be calculated for dysmenorrhea and NMPP separately. An average NRS score for dysmenorrhea is calculated as the average NRS score over the days with menses during a given pain assessment period. An average NRS score for NMPP is calculated as the average NRS score over the days without menses during a given pain assessment period. The analgesic use for a given pain assessment period is summarized by total dose count defined as the average daily dose count taken during the given pain assessment period multiplied by 35. Additional details on calculating dose counts and on the precise definition of an increase in analgesic use will be provided in the SAP.

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

- Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores;
- Change from the parent study Baseline to Week 52/EOT in the mean dysmenorrhea NRS score;
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 52/EOT;
- Change from the parent study Baseline to Week 52/EOT in the mean NMPP NRS score;
- Proportion of patients who are better or much better on the PGIC for NMPP at Week 52/EOT;
- Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia NRS scores;
- Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 52/EOT;
- Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia functional impairment on the sB&B scale;
- Change from the parent study Baseline to Week 52/EOT in severity scores on the PGA for pain;

- Change from the parent study Baseline to Week 52/EOT in function impairment on the PGA for function;
- Change from the parent study Baseline to Week 52/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
- Change from the parent study Baseline pain assessment period to Week 52/EOT in dysmenorrhea-related functional effects (sB&B);
- Change from the parent study Baseline pain assessment period to Week 52/EOT in NMPP-related functional effects (sB&B).

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

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.

The treatment-emergent period will be defined as the period of time from the first dose date of randomized study drug in the parent study 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, 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, high level term, and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

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

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

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. ECGs will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

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

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

Additional analyses will be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Pharmacodynamics Analyses

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

9.7. Exploratory Analyses

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

- Change from Baseline to Week 52/EOT in the EHP-30 scale total score;
- Change from Baseline to Week 52/EOT in the EHP Work Domain score;
- Change from parent study Baseline to Week 52/EOT in the EQ-5D-5L.

9.8. Interim Analyses

There are no planned interim efficacy analyses.

9.9. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

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

investigator. The investigator and sub-investigator agree to notify the sponsor of any change in reportable interests during the study and for 1 year following completion of the study.

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

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

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

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

10.2.2. Study Report

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

10.2.3. Posting of Information on Publicly Available Clinical Trial Registers

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

10.3. Joint Investigator/Sponsor Responsibilities

10.3.1. Access to Information Monitoring

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

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

10.3.2. Access to Information for Auditing or Inspections

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

10.3.3. Study Discontinuation

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

10.3.4. Publications

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

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

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

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.

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APPENDICES

Appendix 1. Protocol-Specified Rescue Analgesics

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.

Country	First-Tier Drug (dose strength)	Second-Tier Drug (dose strength)
Argentina	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Australia	ibuprofen (200 mg)	codeine (30 mg) / paracetamol (500 mg)
Belgium	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Brazil	ibuprofen (200 mg)	codeine (30 mg) / paracetamol (500 mg)
Bulgaria	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Canada	ibuprofen (200 mg)	codeine (30 mg) / acetaminophen (300 mg)
Chile	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Czech Republic	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Finland	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Georgia	ibuprofen (200 mg)	none
Germany	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Hungary	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Italy	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
New Zealand	ibuprofen (200 mg)	30 mg codeine
Poland	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Portugal	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Romania	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
South Africa	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Spain	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
Sweden	ibuprofen (200 mg)	codeine (30 mg) / paracetamol (500 mg)
Ukraine	ibuprofen (200 mg)	tramadol (37.5 mg) / paracetamol (325 mg)
United Kingdom	ibuprofen (200 mg)	codeine (30 mg) / paracetamol (500 mg)
United States	ibuprofen (200 mg)	hydrocodone (5 mg) / acetaminophen (325 mg)

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

Appendix 2. Daily eDiary

Version 3 MY80005-eDiary
US English Screen Report 23May2017

Screen report: my80005-eDiary Subject Facing

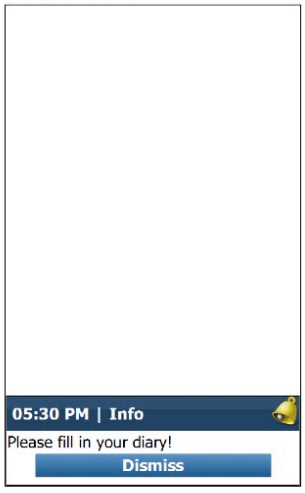
Localized texts are displayed in English.

Contents

Version 3
US English Screen Report

MY80005-eDiary
23May2017

1 Common

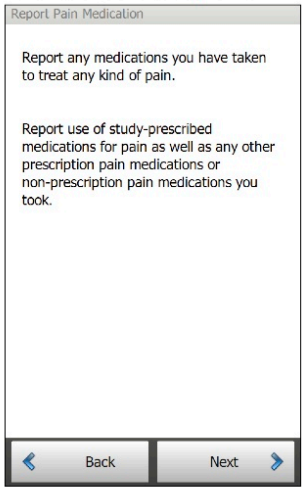


Message 1

Note: Time will populate per device

Version 3 MY80005-eDiary
US English Screen Report 23May2017

2 Form: MedReport



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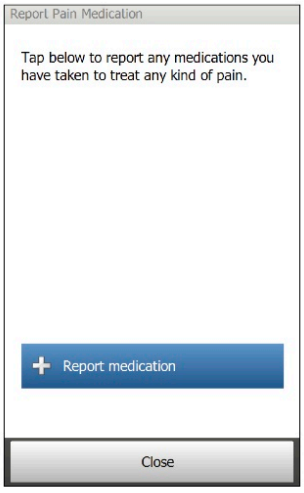

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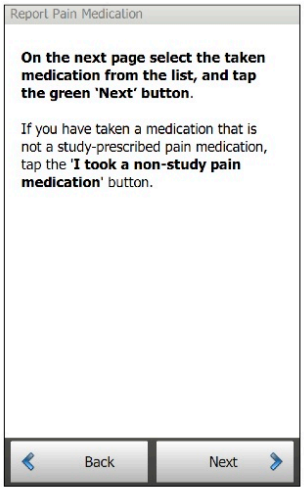

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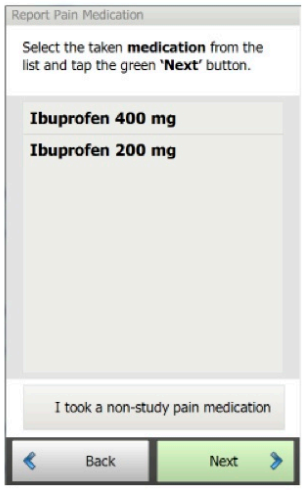


Screen 4

Note: Medications will show per patient set up

Message 1

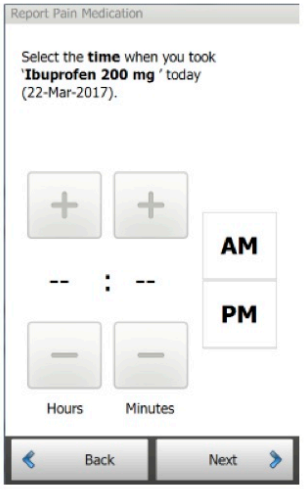
Screen 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2

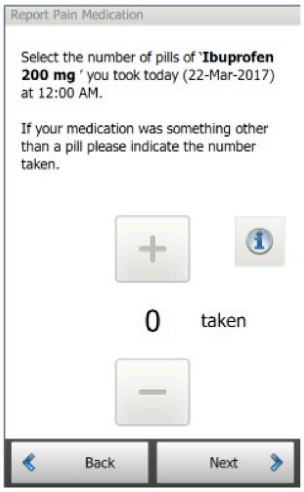


Screen 6

Message 3

Note: Medication Name and Date will show per device

Message 4



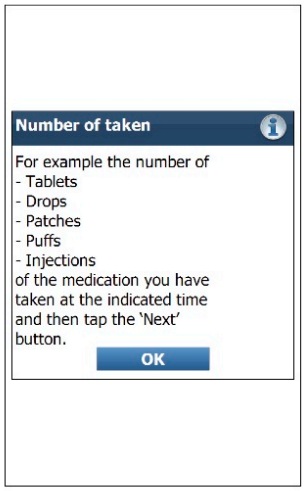
Screen 7

Message 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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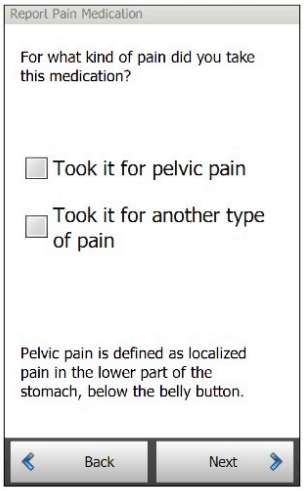

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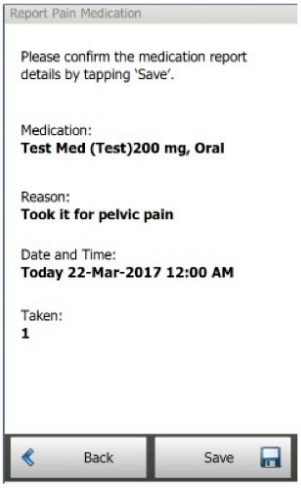
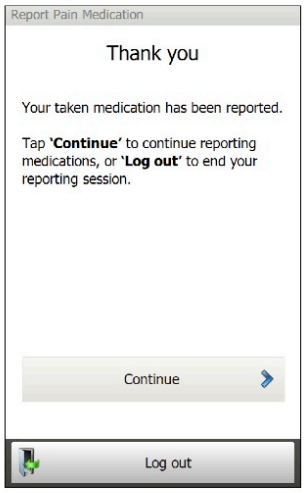


Screen 9

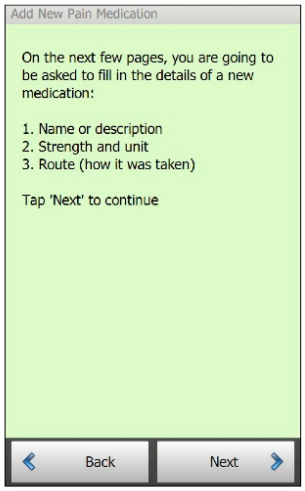
Note: 'Medication', 'Reason', 'Date and Time', 'Taken' will show per patient selection



Screen 10

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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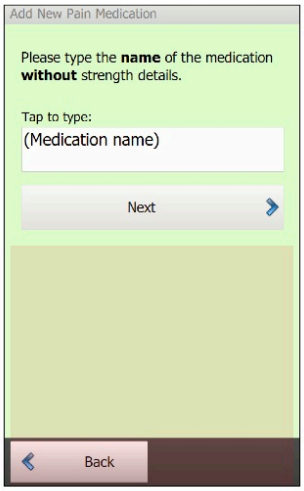
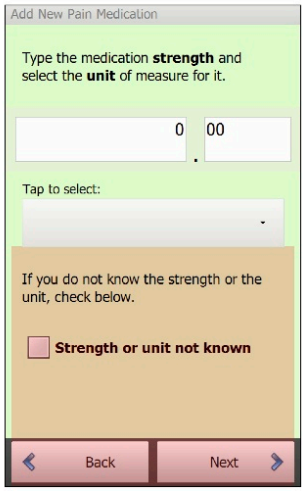


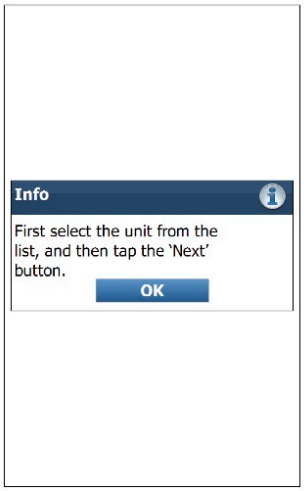
Screen 12

Message 7



Screen 13

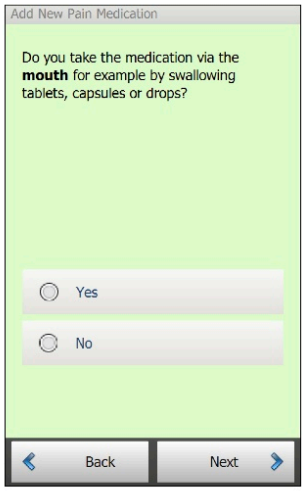
Message 8



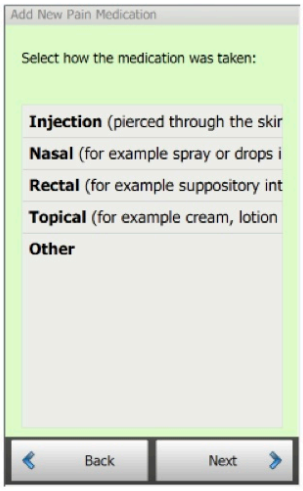
Message 9

Version 3
US English Screen Report

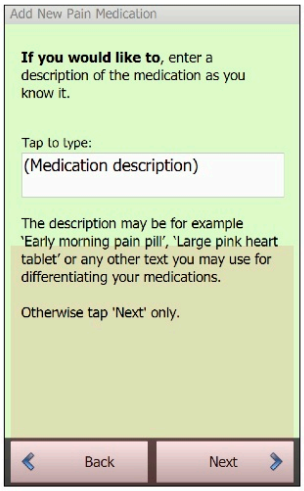
MY80005-eDiary
23May2017



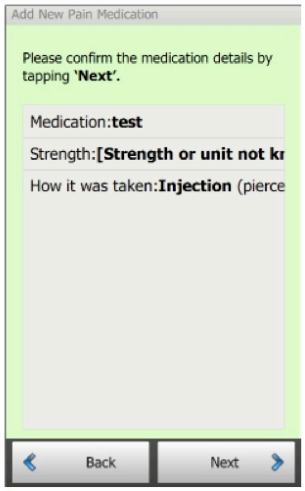
Screen 14



Screen 15



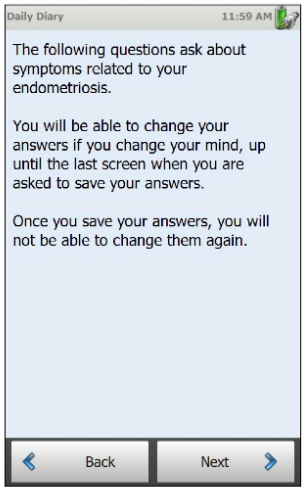
Screen 16



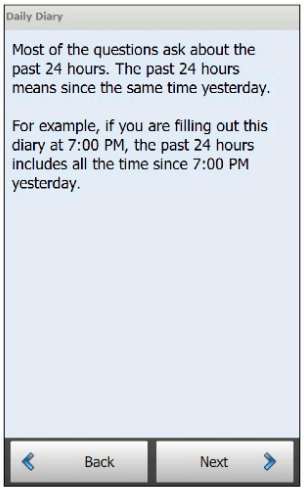
Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

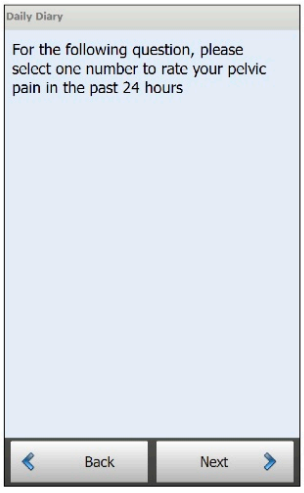
3 Form: Daily Diary



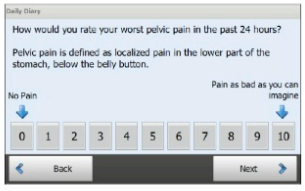
Screen 1



Screen 2

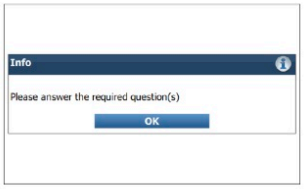


Screen 3



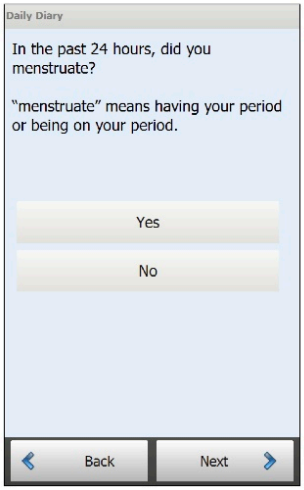
Screen 4

Note: Screen will show latteraly on device



Message 1

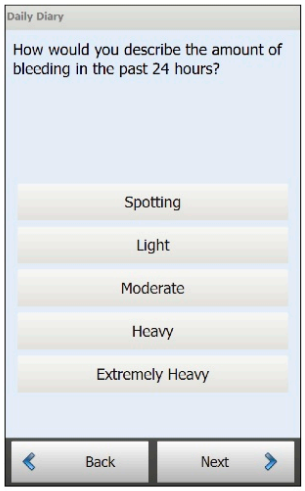
Note: Screen will show latteraly on device



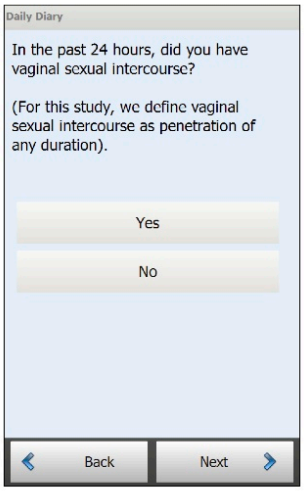
Screen 5

Version 3
US English Screen Report

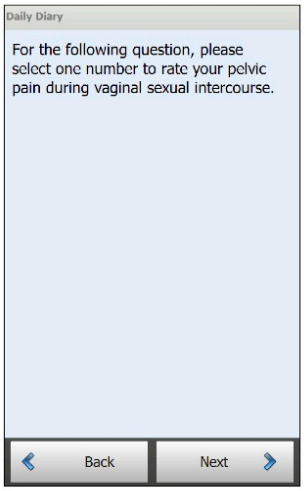
MY80005-eDiary
23May2017



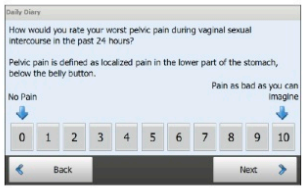
Screen 6



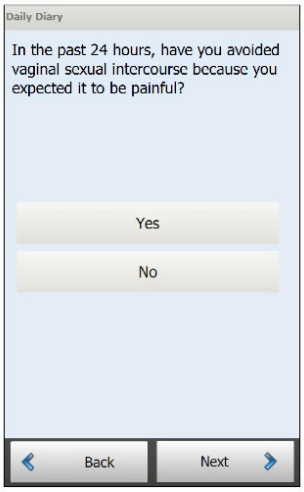
Screen 7



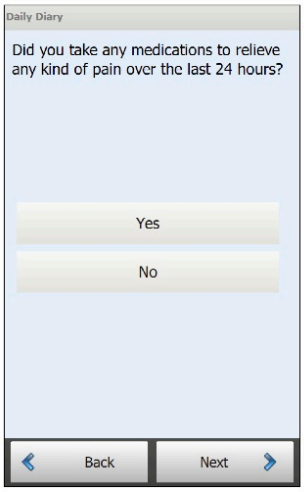
Screen 8



Screen 9



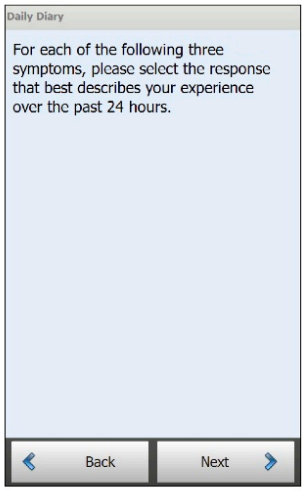
Screen 10



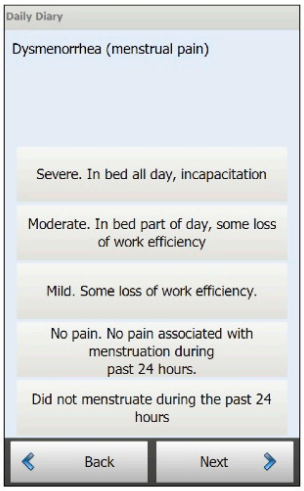
Screen 11

Version 3
US English Screen Report

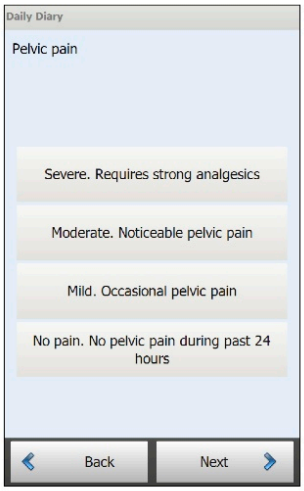
MY80005-eDiary
23May2017



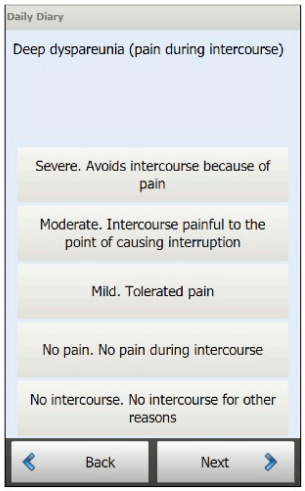
Screen 12



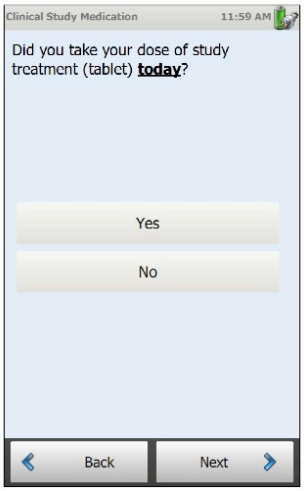
Screen 13



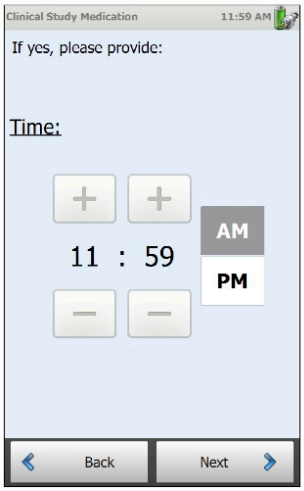
Screen 14



Screen 15



Screen 16

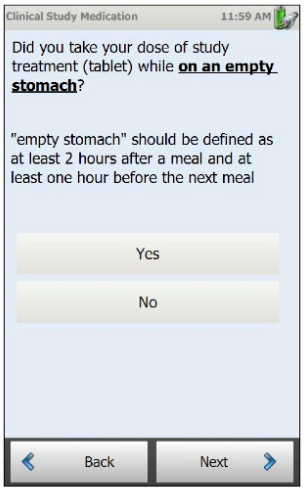


Screen 17

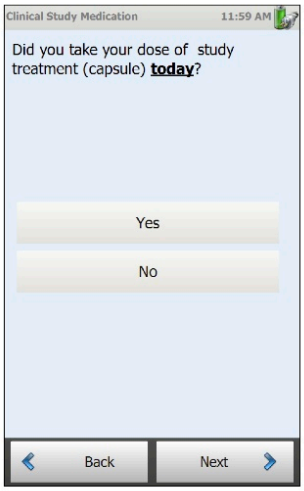
Version 3
US English Screen Report

MY80005-eDiary
23May2017

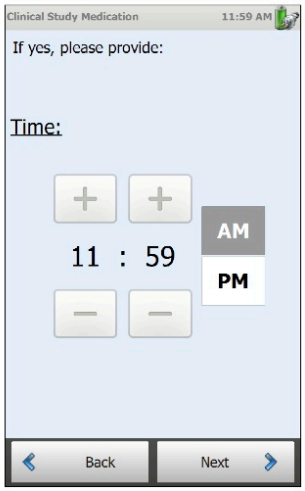
Message 2



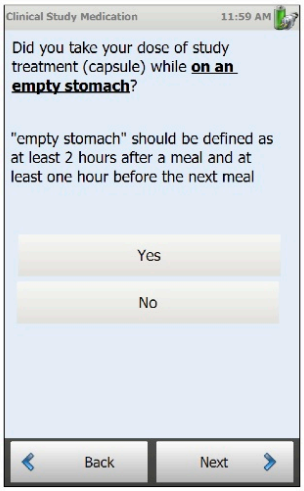
Screen 18



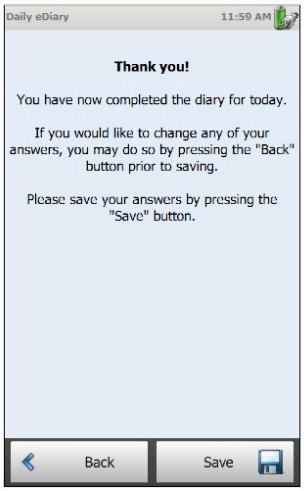
Screen 19



Screen 20



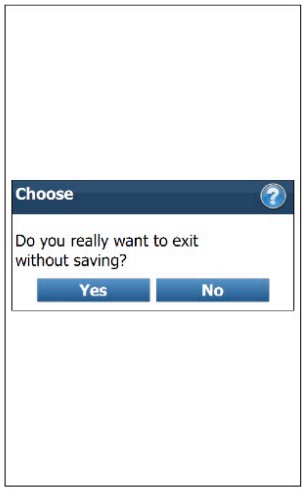
Screen 21



Screen 22

Version 3
US English Screen Report

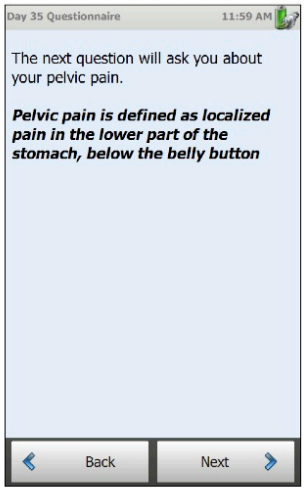
MY80005-eDiary
23May2017



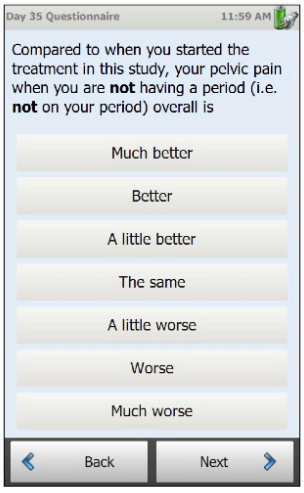
Message 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

4 Form: PGIC-NMPP

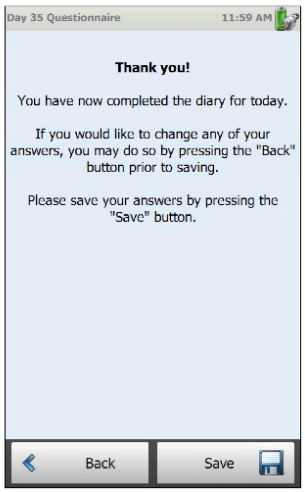


Screen 1



Screen 2

Message 1

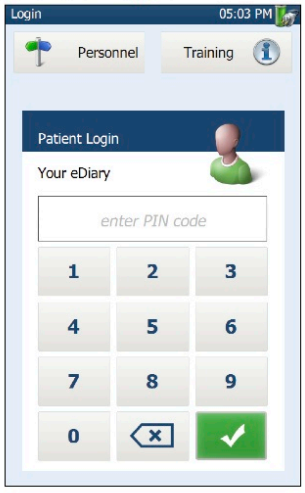


Screen 3

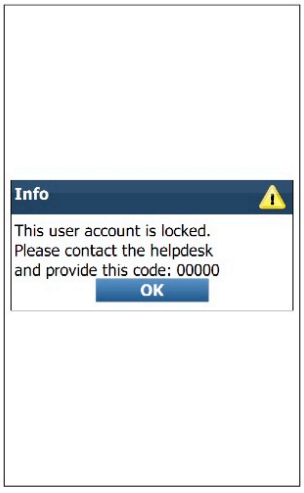
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

5 Form: Login



Screen 1

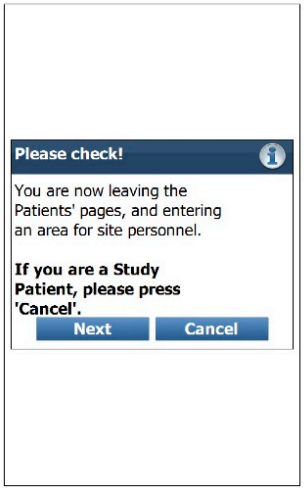


Message 1

Message 2

Message 3

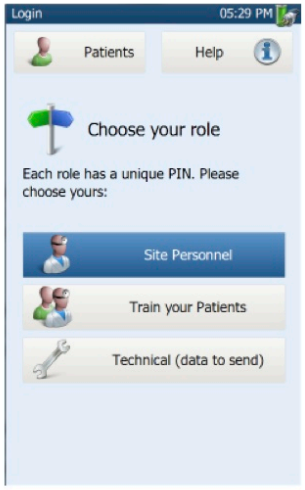
Message 4



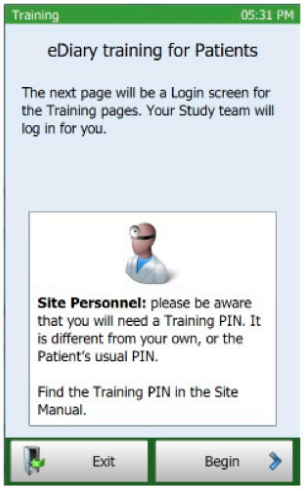
Message 5

Version 3
US English Screen Report

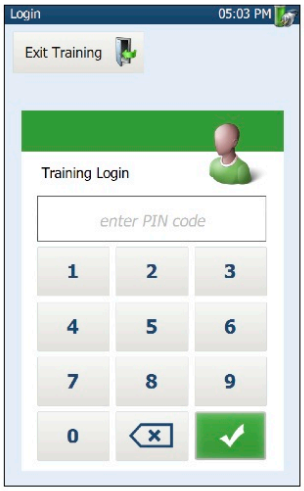
MY80005-eDiary
23May2017



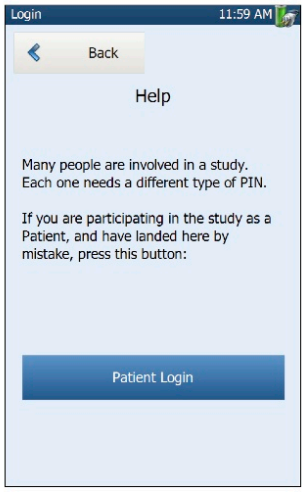
Screen 2



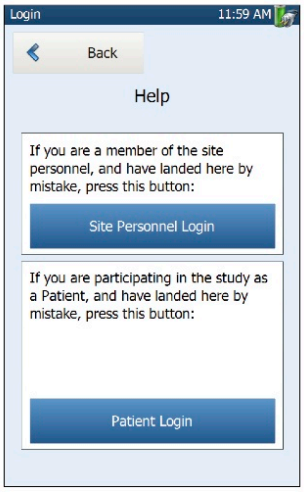
Screen 3



Screen 4



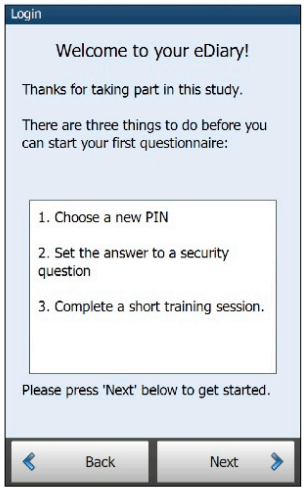
Screen 5



Screen 6

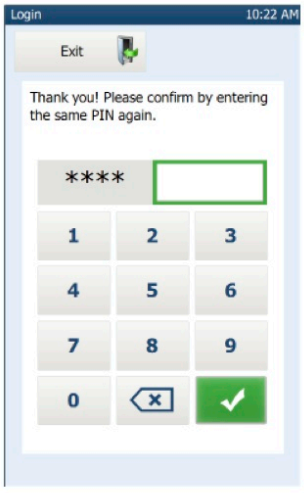
Version 3 MY80005-eDiary
US English Screen Report 23May2017

6 Form: PIN change



Screen 1

Screen 2

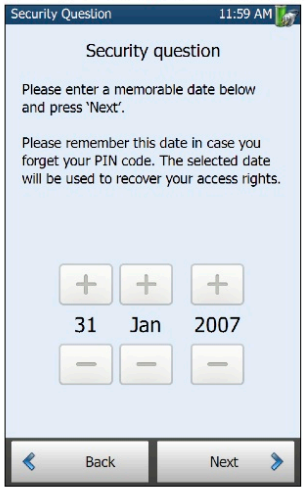


Screen 3

Message 1

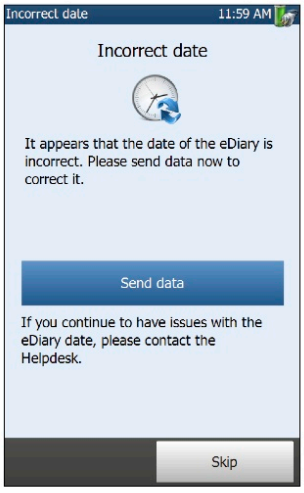
Version 3 MY80005-eDiary
US English Screen Report 23May2017

7 Form: Subject main menu

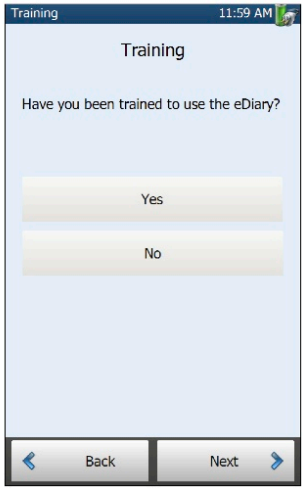


Screen 1

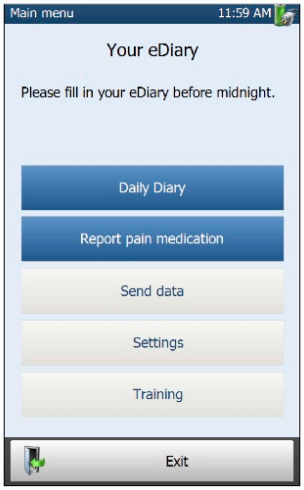
Message 1



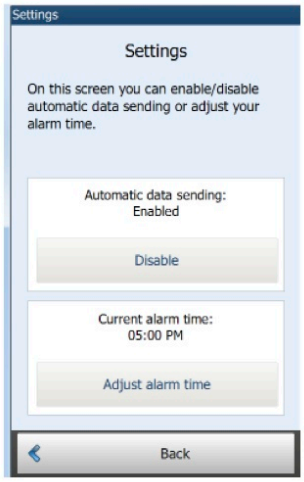
Screen 2



Screen 3



Screen 4



Screen 5

Note: Time will update per device

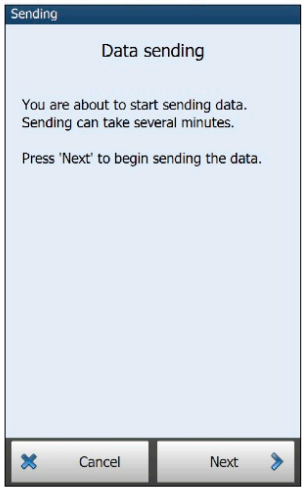
Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

8 Form: Sending



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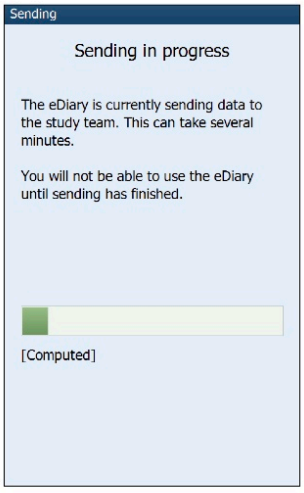

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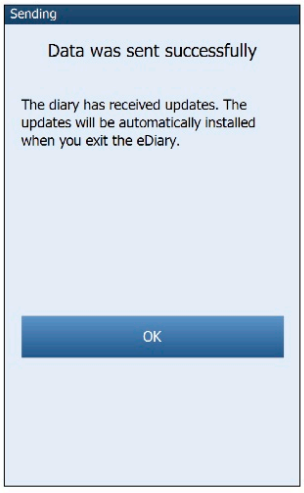

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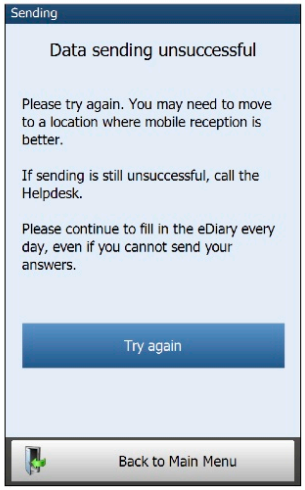

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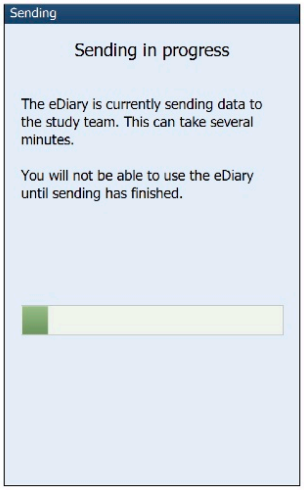

Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017

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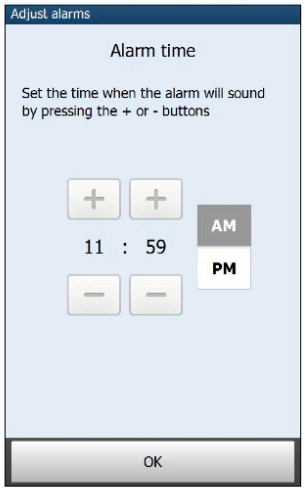

Screen 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

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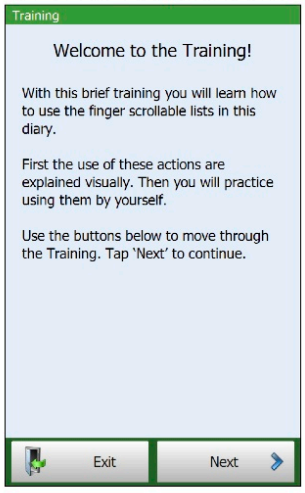
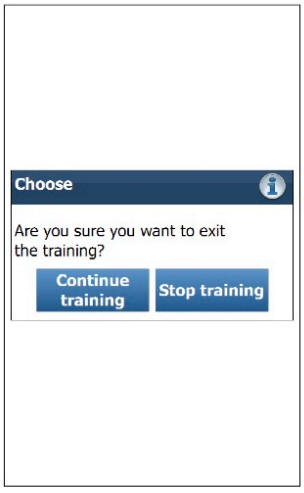


Screen 1

Message 1



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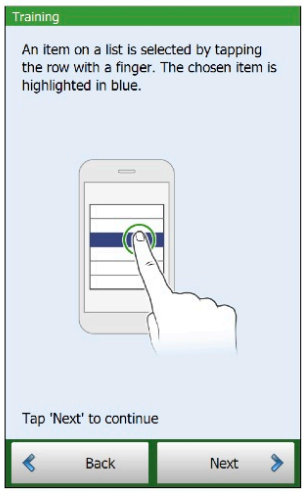
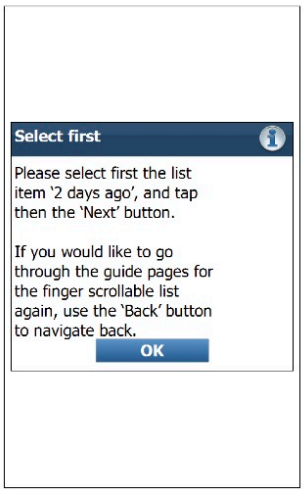


Screen 2

Screen 3



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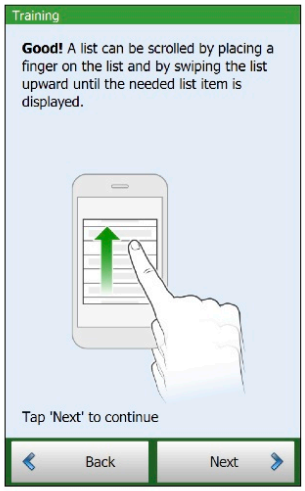
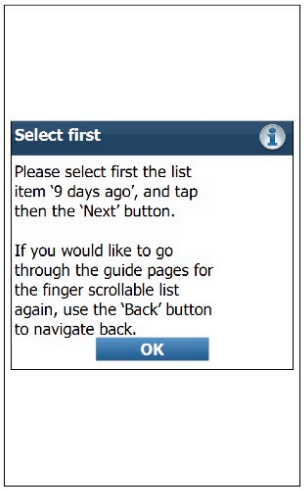
Version 3
US English Screen Report

MY80005-eDiary
23May2017



Screen 4

Screen 5



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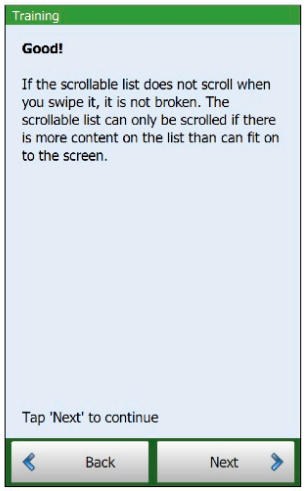

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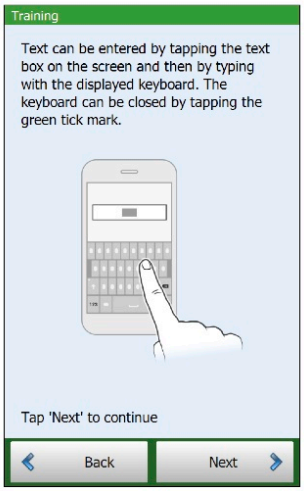

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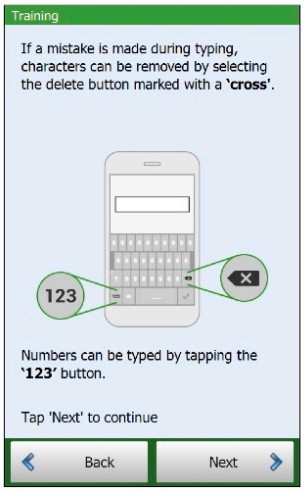

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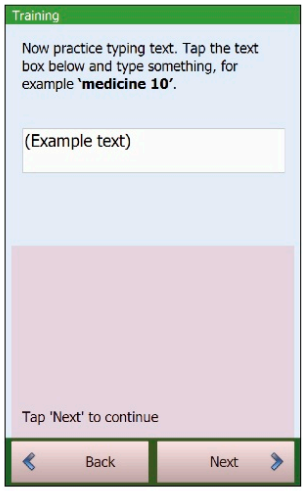
Version 3
US English Screen Report

MY80005-eDiary
23May2017



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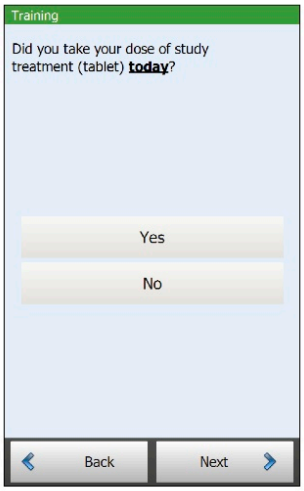

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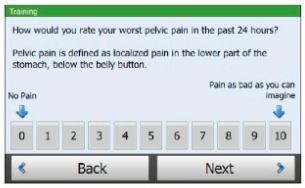

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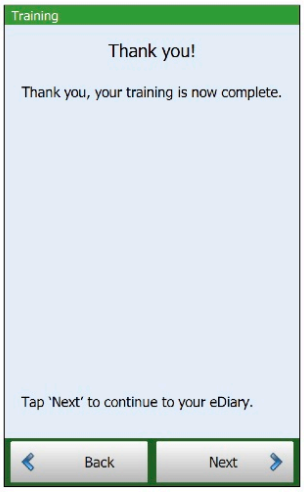


Screen 12

11 Keyboards

Appendix 3. 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 4. 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 ❑

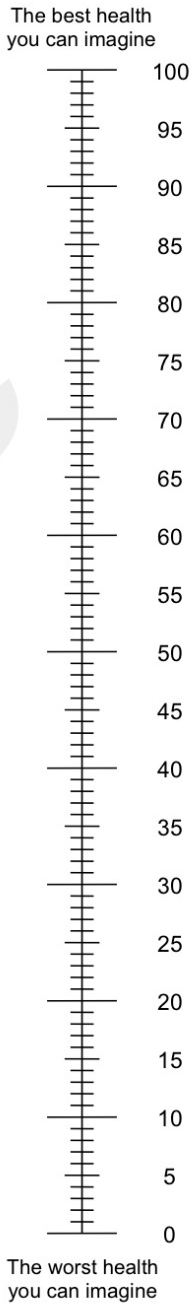
ANXIETY / DEPRESSION

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 5. 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 function)

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

Not at all
Minimally
Moderately
Significantly
Very significantly

Appendix 6. Endometriosis Health Profile - Work Domain

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

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:

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

Recommended tests:

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

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

CBC, complete blood count; INR, international normalized ratio.

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

CLINICAL STUDY PROTOCOL

Study Title:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifiers:	IND# 076642 EudraCT # 2017-004066-10
Version and Effective Date:	Original: 06-NOV-2017 Amendment 1: 20-MAR-2018

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain

Protocol Number: MVT-601-3103

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

PPD

PPD

22-March 2018
Date

PPD

PPD PPD

22 March 2018
Date

PPD

PPD PPD

21 March 2018
Date

PPD

PPD PPD

21 Mar 2018
Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dihyroepiandrosterone
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
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
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NMPP	nonmenstrual pelvic pain
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PLD	phospholipidosis
QTc	corrected QT (interval)
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
sB&B	Subject Modified Biberoglu and Behrman
ULN	upper limit of normal
US	United States

Term	Explanation
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Protocol Number	MVT-601-3103
Location	Multinational, including North and South America, Europe, Africa, New Zealand, and Australia
Study Centers	Approximately 320 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with endometriosis-associated pain
Number of Patients Planned	Approximately 800
Study Objectives	In women with endometriosis-associated pain, the study objectives are as follows: <u>Primary Efficacy Objective</u> • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.

	Secondary Efficacy Objectives • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: o Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; o Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea; o Patient Global Impression of Change (PGIC) for dysmenorrhea; o Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; o PGIC for NMPP; o Dyspareunia, measured by the NRS; o PGIC for dyspareunia; o Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]); o Patient Global Assessment (PGA) for pain; o PGA for function; o Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains; o Dysmenorrhea-related functional effects (sB&B); o NMPP-related functional effects (sB&B). Safety Objectives • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: o Adverse events; o Changes in bone mineral density. Pharmacodynamic Objective • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.

	Exploratory Objective • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).

Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 28 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study, and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit, and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks.

During the 28-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the electronic diary (eDiary). Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).

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

Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit (or most recent scan, if the Week 52/ET scan was not done) relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (±1) months after the last dose of study medication.

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

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

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.
3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;

e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study.

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;
6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

Note: Visual acuity score must have been obtained with corrective lenses, if applicable. 12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor; 13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).	
Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 28 weeks (Open-Label Treatment Period). Concomitant Medicinal Products Systematically Prescribed for All Study Patients Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug and a second-line opioid or opioid/acetaminophen or opioid/paracetamol combination for endometriosis-related pain relief as required. The specific analgesic drugs offered may differ for different countries or regions. The analgesics for each patient will be the same as those prescribed for her during the parent study.
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study. Primary Efficacy Endpoints • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores.

	Secondary Efficacy Endpoints • Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores; • Change from the parent study Baseline to Week 52/end of treatment (EOT) in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 52/EOT; • Change from the parent study Baseline to Week 52/EOT in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP at Week 52/EOT; • Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 52/EOT; • Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline to Week 52/EOT in severity scores on the PGA for pain; • Proportion of responders at Week 52/EOT based on their EHP-30 Pain Domain score; • Change from the parent study Baseline to Week 52/EOT in function impairment on the PGA for function; • Change from the parent study Baseline to Week 52/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period to Week 52/EOT in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period to Week 52/EOT in NMPP-related functional effects (sB&B). Safety Endpoints • Incidence of adverse events; • Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. Pharmacodynamic Endpoint • Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol. Exploratory Endpoints • Change from Baseline to Week 52/EOT in the EHP-30 scale total score; • Change from Baseline to Week 52/EOT in the EHP Work Domain score; • Change from parent study Baseline to Week 52/EOT in the EQ-5D-5L.

Statistical Methods

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

Efficacy

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

The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

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

Safety

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

Drug exposure will be summarized by descriptive statistics. Severity of all treatment-emergent adverse events will be evaluated by the investigator based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and will be coded to preferred term, high level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values will be classified by toxicity grade based on the National Cancer Institute CTCAE. Laboratory shift tables of the parent study Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits. The absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change at Week 52 from parent study Baseline in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3101 or MVT-601-3102) and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3103

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Informed Consent	X[d]									
Review Eligibility Criteria	X									
Concomitant Medications[e]	X[f]	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X[g]	X	X	X	X	X	X	X	X[h]	X
Weight	X[g]			X				X	X[h]	
Complete Physical Exam	X[g]							X	X[h]	
Visual Acuity[i]	X[g]									
Signs and Symptoms-Directed Physical Exam[j]		X	X	X	X	X	X		X[h]	X
12-Lead ECG[k]	X[g]							X	X[h]	
Clinical Laboratory Tests[l]	X[g,m]	X	X	X	X	X	X	X[m]	X[h]	X
Pharmacodynamics Sample[n]	X[g,m]							X[m]	X[h,m]	
Urinalysis	X[g]							X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X[h]	X

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Daily eDiary[o]	X[g]	X	X	X	X	X	X	X		X
Site Review of eDiary Data	X[g]	X	X	X	X	X	X	X	X[h]	X
Bone Densitometry[p]	X[g]			X				X[q,r]	X[h]	
Endometrial Biopsy	X[g,s]								X[h]	
Dispense Study Treatment	X	X	X	X	X	X	X		X[h]	
Dispense or prescribe protocol-specified analgesic drugs[t]	X	X	X	X	X	X	X	X	X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic	X[u]							X	X[h]	
Daily Self-Administration of Study Treatment[v]		X								
Take Protocol-specified Rescue Analgesics as Needed[w]	X									
EHP-30 Questionnaire[x]	X[g]			X			X	X	X[h]	
Patient Global Assessment for Pain[x]	X[g]	X	X	X	X	X	X	X	X[h]	
[on paper] Patient Global Assessment for Function[y]	X[g]	X	X	X	X	X	X	X	X[h]	
Patient Global Impression of Change[x]	X[g]			X				X	X[h]	

PERIOD	OPEN-LABEL TREATMENT									SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 52[a] (or Early Termination of Study Drug)**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
[on paper] EHP Work Domain[y]	X[g]							X	X[h]	
EQ-5D-5L Questionnaire[x]	X[g]							X	X[h]	
Adverse Event Collection[z]	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery										X[aa]

Abbreviations: BP, blood pressure; DXA, dual-energy x-ray absorptiometry; ECG, electrocardiogram; eDiary, electronic diary; EHP, Endometriosis Health Profile; EQ-5D-5L, European Quality of Life Five-Dimension Five-Level Scale; exam, examination; HR, heart rate; NRS, Numerical Rating Scale; sB&B, Subject Modified Biberoglu and Behrman.

a. The Week 52 visit should occur on or after the 1-year anniversary of Study Day 1 of the parent study.
b. Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.
c. The Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit.
d. May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3103 is defined by administration of the first dose of MVT-601-3103 study drug.
e. Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up Period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3103 should be reported as concomitant medications in the parent study (MVT-601-3101 or MVT-601-3102). If concomitant medication is ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.
f. Concomitant medications are recorded both for the parent study and for MVT-601-3103 at the Week 24/Baseline visit. (See footnote e for further details).
g. This is a parent study (MVT-601-3101 or MVT-601-3102) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3103 and is covered under the informed consent for the parent study.
h. The indicated procedure may be performed at the Unscheduled visit based on the purpose of the visit (eg, follow-up for an adverse event or abnormal laboratory test).
i. See parent study protocols (MVT-601-3101 or MVT-601-3102) for instructions on testing visual acuity.
j. The exam may include a gynecologic examination, if indicated based on signs and symptoms.
k. The 12-lead ECGs will be submitted for central reading.
l. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, and Week 52. At the Week 24/Baseline visit and Week 52 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.
m. Samples should be obtained in a fasted state (at least 8 hours). Water is allowed during the fasting period.

n. For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week 52/Early Termination, collect samples for analysis of estradiol concentrations only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are completed.
o. At the Week 24/Baseline visit, transition the patient within her eDiary from the parent study to MVT-601-3103. The eDiary data collection will include NRS pain scores, menstruation information (including severity of bleeding), analgesic drug use, date and time of study drug administration, and sB&B scale scores.
p. Bone densitometry (L1-L4, total hip, femoral neck) will be submitted for central reading.
q. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within 4 weeks after completion of the Week 36 scan. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.
r. Patients with a bone mineral density loss of > 3% at their Week 52/Early Termination visit (or most recent scan if the Week 52/Early Termination visit was not done) relative to parent study Baseline measurement will undergo a follow-up bone densitometry scan at 6 (±1) months and will be contacted to question them about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.
s. Endometrial biopsies are to be done per instructions in the parent study. See the Laboratory Manual for guidance on handling and shipping the biopsy sample to the central laboratory for analysis. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details).
t. Please see Appendix 1 for list of protocol-specified analgesics and see the Study Reference Manual for information on where and how to obtain protocol-specified analgesic medications by country. At the Week 52 visit, patients who will not be proceeding to another 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 another extension study, refer to the protocol for that next study.
u. Pregnancy test must be negative before the study drug dose is administered.
v. Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week 52/Early Termination visit.
w. Patients may only take their study-specified analgesics for pain. Analgesics should **not** be taken prophylactically (ie, in anticipation of pain).
x. The patient will enter her response(s) into an electronic 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.
y. The patient will enter her response onto a paper questionnaire at the site. Paper questionnaires should be done in the following order: PGA for function, EHP Work Domain.
z. Collect adverse events from the time that the first dose of study drug for MVT-601-3103 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3103 should be reported as an adverse event in the parent study (MVT-601-3101 or MVT-601-3102). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.
aa. Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted again by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.

2. INTRODUCTION

2.1. 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 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

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

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once-daily oral medication for the treatment of 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 was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

3. STUDY OBJECTIVES AND ENDPOINTS

Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week 52) for the following parent study treatment groups:

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

The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study.

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

Objectives	Endpoints

Objectives	Endpoints
Primary Efficacy	
• To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	• Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores.
Secondary Efficacy	
To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following:	
• Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain;	• Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores;
• Dysmenorrhea, as measured by the NRS for dysmenorrhea;	• Change from the parent study Baseline to Week 52/end of treatment (EOT) in the mean dysmenorrhea NRS score;
• Patient Global Impression of Change (PGIC) for dysmenorrhea;	• Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 52/EOT;
• NMPP, as measured by the NRS for NMPP;	• Change from the parent study Baseline to Week 52/EOT in the mean NMPP NRS score;
• PGIC for NMPP;	• Proportion of patients who are better or much better on the PGIC for NMPP at Week 52/EOT;
• Dyspareunia, measured by the NRS;	• Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia NRS scores;
• PGIC for dyspareunia;	• Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 52/EOT;
• Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]);	• Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia functional impairment on the sB&B scale;

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 function measured by the Endometriosis Health Profile (EHP)-30 Pain Domain;	• Proportion of responders at Week 52/EOT based on EHP-30 Pain Domain scores;
• Patient Global Assessment (PGA) for pain;	• Change from the parent study Baseline to Week 52/EOT in severity scores on the PGA for pain;
• PGA for function;	• Change from the parent study Baseline to Week 52/EOT in function impairment on the PGA for function;
• Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains;	• Change from the parent study Baseline to Week 52/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
• Dysmenorrhea-related functional effects (sB&B);	• Change from the parent study Baseline pain assessment period to Week 52/EOT in dysmenorrhea-related functional effects (sB&B);
• NMPP-related functional effects (sB&B).	• Change from the parent study Baseline pain assessment period to Week 52/EOT in NMPP-related functional effects (sB&B).
Safety	
To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	
• Adverse events;	• Incidence of adverse events;
• Changes in bone mineral density.	• Percent change from the parent study Baseline to Week 52 in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).

Objectives	Endpoints
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	• Change from parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol.
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 52-weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	• Change from Baseline to Week 52/EOT in the EHP-30 scale total score; • Change from Baseline to Week 52/EOT in the EHP Work Domain score; • Change from parent study Baseline to Week 52/EOT in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 28 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 52 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study, and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been

completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit, and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 28 weeks.

During the 28-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the electronic diary (eDiary). Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via DXA.

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

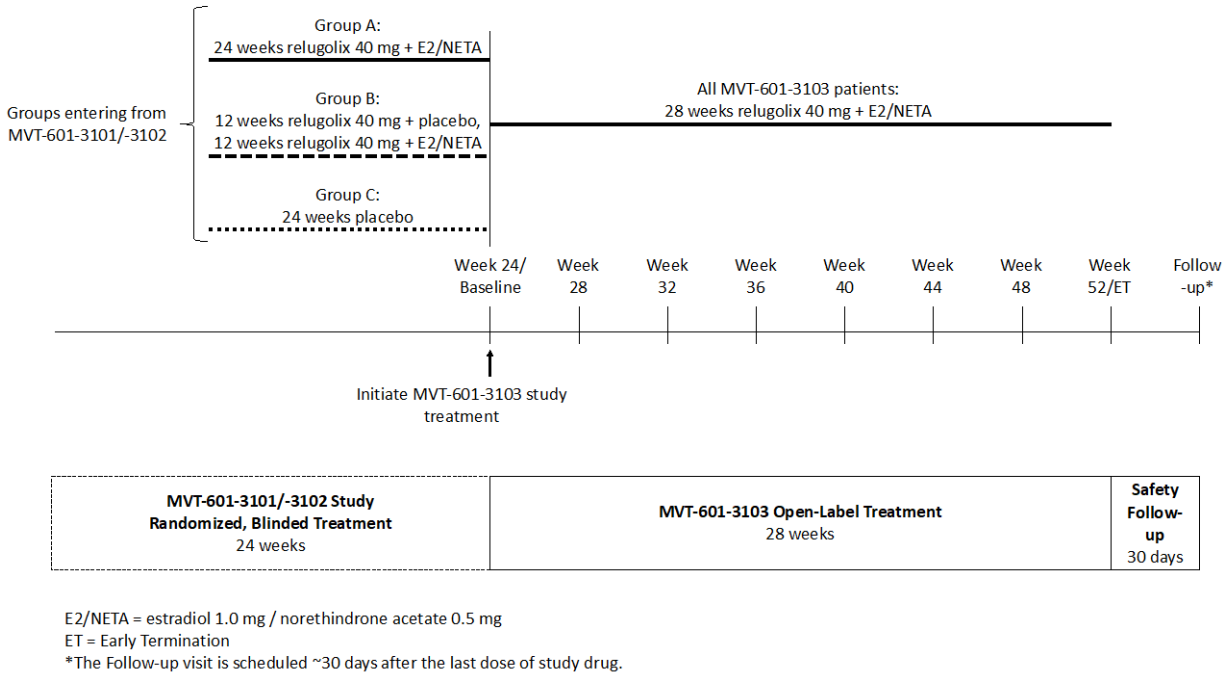
Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit (or most recent scan, if the Week 52/ET scan was not done) relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months after the last dose of study medication.

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

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

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

Figure 4-1 MVT-601-3103 Study Schematic



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

4.2. Discussion of Study Design, Including Dosing

The SPIRIT EXTENSION study (MVT-601-3103) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3101 and MVT-601-3102) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with endometriosis-associated pain. This 28-week extension study provides additional efficacy and safety data up to 52 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily (N = 101) suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids

demonstrated the 40-mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 52 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 52 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2017; Lee, 2016; Franke, 2000] or endometriosis-associated pain [Wu, 2014]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the United States (US) as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol

concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3101 and MVT-601-3102) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a significant decrease in endometriosis-associated pain in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose estradiol and norethindrone acetate to decrease dysmenorrhea and NMPP and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 28 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102). This study design will allow eligible patients with endometriosis-associated pain, who were randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 800 premenopausal women aged 18 to 51 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. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.

3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable nonhormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified nonhormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a nonhormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;

6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. The presenting visual acuity score has decreased by 10 or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.
12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor;
13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).

4.4. Method of Assigning Patients to Treatment Group and Patient Identification Number

Eligible patients who sign consent will be identified with the same Patient Identification (ID) Number assigned to the patient during the parent study. This extension study is a single-arm

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

4.5. Removal of Patients from Therapy

Completion of the Week 52 visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 52 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication). 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 enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
    - ALT or AST > 8 x ULN; or
    - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
    - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
    - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);
- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. 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 of eDiary completion. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;

- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

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

4.6. Contraception/Pregnancy Avoidance

In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use nonhormonal contraception throughout the study 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 Week 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™) at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Has a nonhormonal intrauterine device (eg, Paragard®) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of nonhormonal contraception as described below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

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

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

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

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

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

5. TREATMENTS

5.1. Treatments Administered

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

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

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

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

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

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 1. 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 common excipients.

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

5.3. Randomization and Stratification

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

5.4. Directions for Administration

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

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

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

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. 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. Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Study Reference Manual and Pharmacy 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 lot/batch 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 and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the Study Reference Manual.

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. The study-specified pain medications for each patient will be the same as for the parent study. Only study-specific Tier 1 and Tier 2 analgesic medications (see Appendix 1) should be taken starting with the Baseline/Week 24 visit and subsequently. Analgesic medications will be taken for control of pain and not prophylactically.

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 at the time of enrollment into this study. 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 the time of enrollment in this study, 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.

5.8. Blinding

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

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 Week 24/Baseline visit and Week 52/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 study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Because of the importance to both safety and efficacy evaluation, patients who are grossly noncompliant with eDiary completion must undergo an Unscheduled visit to evaluate reasons for noncompliance 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 4.5 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. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 5-2 are prohibited at any time during the study through the Follow-Up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-2 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	
GnRH analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-androgens	danazol	
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	Note: All other anticonvulsants are allowed
Aromatase inhibitors	anastrozole letrozole	
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective estrogen receptor modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective progesterone receptor modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine devices	levonorgestrel copper	

Drug Class	Examples	Comments
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir[f]	Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Drug Class	Examples	Comments
Moderate and strong P-glycoprotein inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	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.
Analgesic drugs **other** than those specified for use during the study[l]	Acetaminophen/paracetamol (other than any included in a study-specified analgesic) aspirin > 325 mg/day NSAIDs (other than study-specified NSAIDs) gabapentin pregabalin carbamazepine metamizole	Note: Aspirin ≤ 325 mg per day is allowed
Antidepressants New treatment or changed doses of SSRI, SNRI, or TCA antidepressants	**SNRI examples:** duloxetine venlafaxine desvenlafaxine **SSRI examples:** citalopram fluoxetine paroxetine fluvoxamine **TCA examples:** amitriptyline doxepin desipramine nortriptyline	SSRI, SNRI, or TCA allowed if given at the same dose as used during the 3 months prior to the Run-In Period of MVT-601-3101 or MVT-601-3102. 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.

Abbreviation: GnRH, gonadotropin-releasing hormone; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; 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

5.10.2. Permitted Medications

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

5.10.2.1. Analgesics

All analgesics will be collected in the eDiary and recorded in the electronic Case Report Forms (eCRFs).

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of endometriosis is prohibited from the Week 24/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Study Reference Manual.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 2 periods: Open-Label Treatment Period and Safety Follow-Up Period. Unscheduled visits may occur as needed to evaluate patients.

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

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3101 or MVT-601-3102 will serve as the Week 24/Baseline procedures for patients

who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

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

- Informed consent (unless signed previously);
- Record concomitant medications;
- Update the patient's status in the IVRS/IWRS as being in the MVT-601-3103 and receive the lot numbers for study drug allocation;
- Dispense study treatment;
- Dispense or prescribe protocol-specified analgesic drugs;
- Transition the patient within her eDiary from the parent study to MVT-601-3103
- Take study drug dose in clinic; and
- Record adverse events, if any.

The Week 24 visit date in the parent study is defined as the date that the last procedures for the Week 24 visit were completed, acknowledging that the Week 24 visit procedures may be completed on different dates. Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit, and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit.

Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, and 52. Sites will monitor diary completion using the TrialManager web portal throughout the study.

Accountability for study drug will be performed at each visit. Instructions for analgesic medication usage will be reinforced at each visit.

Questionnaires are administered on the electronic tablet and on paper at each visit. These procedures should occur before any other types of study procedures are performed. When both electronic tablet and paper questionnaires are required at a visit, 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 function
  - EHP Work Domain [Week24/Baseline and Week 52 only]

Patients will bring their eDiary, analgesic medications, and study drug to each visit. The site must document the start and stop dates of the patient's menses.

An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details). Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, and Week 52. At the Week 24/Baseline visit and Week 52 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.

ECGs will be done at the Week 24/Baseline and at the Week 52/Early Termination visits. Bone densitometry will occur at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits. Week 52/Early Termination.

Bone densitometry and ECGs will be submitted for central reading.

Study drug compliance will be reviewed at each visit. Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

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

6.3. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 52 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 52; however, for patients whose last dose of study drug is during Week 32 or earlier or within 4 weeks after completion of the Week 36 scan, the bone densitometry 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(s).

Patients (including those who complete the Week 52 visit and those who withdraw early from this study) will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week 52 visit, the Follow-up visit may be waived.

The Follow-up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (see Section 1.1) for individual study visit procedures during the Follow-up visit.

6.4. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the

investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, symptom-directed brief physical examination, central safety laboratory assessment, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Pharmacodynamics Sample Collection

A blood sample for the pharmacodynamic analysis of serum estradiol will be collected pre-dose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week 52 or the Early Termination visit, when no dose is administered. These pharmacodynamic samples will be analyzed at a central laboratory. These results will not be shared with the sites at any time.

6.5.1.2. Patient eDiary

All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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.

6.5.1.3. 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 3). Patients will complete the EHP-30 questionnaire at the site at visits indicated in Section 1.1 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.

6.5.1.4. 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 4). 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 visits indicated in Section 1.1 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.

6.5.1.5. 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 5) 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. The PGA for pain severity and the PGIC will be completed on a tablet device at the study site. The PGA for function will be completed on a paper questionnaire at the study site.

6.5.1.6. 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 6). Patients will complete the EHP Work Domain questionnaire at visits indicated in Section 1.1 before other types of study procedures, such as blood draws and physical examinations, are performed. The EHP Work Domain will be completed on a paper questionnaire at the study site.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

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

6.5.2.2. Vital Signs

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

6.5.2.3. Physical Exams

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment.

6.5.2.4. 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
Creatine kinase		Urine Microscopy (reflex testing based on abnormal urine analysis)
Hemoglobin A1c		
Bilirubin total		
Alanine aminotransferase		
Aspartate aminotransferase		
Gamma-glutamyl transferase		
Alkaline phosphatase		
Hormones	**Lipids**	**Pregnancy**
Estradiol	Total cholesterol	Pregnancy test (human chorionic gonadotropin)
	Low density lipoprotein	
	High density lipoprotein	
	Triglycerides	

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, 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.

6.5.2.5. 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 the central core laboratory with the patient in a semi-supine or supine position after 5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3 and L4), total hip, and femoral neck (same leg within each patient) at the time points described in the Schedule of Activities (Section 1.1). The scans will be read by the central imaging laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient and should be the same as used for the patient during the parent study (MVT-601-3101 and MVT-601-3102). The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study.

Patients with a bone mineral density loss of > 3% at lumbar spine or total hip at their Week 52/Early Termination visit (or most recent scan if the Week 52/ET scan was not done) relative to parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months and will be contacted to obtain information about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.

Patients who experience a bone mineral density loss from the parent study Baseline of ≥ 7% at any of the anatomical sites assessed will be discontinued from the extension study and will undergo another bone densitometry scan as described above. Patients should be assessed for secondary causes of bone loss and followed up further if not improving on the 6-month follow-up scan, unless an alternative etiology has been identified.

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

6.5.2.7. Status of Menstruation Recovery

If the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 52 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

7. SAFETY CONSIDERATIONS

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

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 admitted to a hospital, independent of the duration of that hospitalization. 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 and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another

investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

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

7.3. Assigning Causal Relationship to Study Drug

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

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

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

7.4. Assigning Severity Rating for Adverse Events

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

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

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

Grade	Criteria
1/Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated

2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3/Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4/Life-threatening	Life threatening consequences; urgent intervention indicated
5/Death	Death related to adverse event

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

7.5. Adverse Events of Clinical Interest Reporting

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

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

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

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

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

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the 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-601-3103);
- Site address and number;
- Investigator name;
- Patient ID number, sex, and age;
- Details of study drug administration;
- The date of the report;
- A description of the serious adverse event (event term, seriousness of the event, date of onset, intensity);
- Causal relationship to the study drug.

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

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

7.7. Study Drug Overdose Management

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

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

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

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

- Contact the medical monitor immediately;
- Closely monitor the patient for adverse events and laboratory abnormalities;
- All overdose events are to be reported within 24 hours of awareness by the study site, using a serious adverse event form according to Section 7.6, whether or not the overdose is associated with an adverse event;
- If possible, obtain a plasma sample for pharmacokinetic analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

7.8. Pregnancy Reporting

If any patient becomes pregnant during the study, the site must discontinue the patient from the study treatment immediately and have her return for an Early Termination visit.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy 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 form, as available.

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

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

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on 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 (corrected QT [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD), reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

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

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the parent studies.	Bone mineral density will be monitored at the Week 24/Baseline, Week 36, and Week 52/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the parent studies.	12-lead ECG at the Week 24/Baseline and Week 52/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal liver test results (AST or ALT > 3 x ULN) that develop during the Open-Label Treatment Period will be reported within 24 hours of study personnel awareness.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with phospholipidosis (PLD). PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 24/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

8. DATA QUALITY ASSURANCE

8.1. Clinical Procedures

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

8.2. Monitoring

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

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

Adverse events and concomitant medications terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary Enhanced (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 (SAP) will describe the detailed statistical methods and analyses for this study.

All efficacy and safety measures over the course of both the parent and extension studies will be presented by the parent study treatment group using descriptive statistics. No formal treatment comparisons will be performed for this extension study. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

9.1. Randomization Methods

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

9.2. Analysis Populations

Efficacy data analyses will be performed on the modified Intent-to-Treat (mITT) Population, defined as all patients who were randomized in a parent study (MVT-601-3101 or MVT-601-3102) and who have received any amount of randomized study drug.

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

The analysis methods for safety and efficacy endpoints are the same as those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Justification

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

9.4. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the mITT Population.

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

The point estimates and 2-sided 95% confidence intervals (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline. Patients who had a pain reduction less than the pre-determined threshold or who had an increase in the use of analgesics for endometriosis-associated pain will be considered non-responders. The pain reduction thresholds will be determined for NMPP and dysmenorrhea separately (see the SAP for details) for the parent studies and these same thresholds will be applied to this study.

Baseline values are calculated using the Baseline pain assessment period, which is defined as the period from the date of the first dose of placebo in the parent study Run-In Period through the day prior to the first dose of randomized study drug. Patients' average NRS pain scores and use

of rescue analgesic medications for endometriosis-associated pain (dysmenorrhea or NMPP) will be compared between a given visit-specific pain assessment period (eg, Week 28, Week 32, etc.) and the Baseline pain assessment period. The visit-specific pain assessment period is defined as the last 35 calendar days immediately prior to and including the last dose of study drug treatment received prior to the visit date.

For any pain assessment period (Baseline or visit-specific), the average NRS scores will be calculated for dysmenorrhea and NMPP separately. An average NRS score for dysmenorrhea is calculated as the average NRS score over the days with menses during a given pain assessment period. An average NRS score for NMPP is calculated as the average NRS score over the days without menses during a given pain assessment period. The analgesic use for a given pain assessment period is summarized by total dose count defined as the average daily dose count taken during the given pain assessment period multiplied by 35. Additional details on calculating dose counts and on the precise definition of an increase in analgesic use will be provided in the SAP.

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

- Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores;
- Change from the parent study Baseline to Week 52/EOT in the mean dysmenorrhea NRS score;
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea at Week 52/EOT;
- Change from the parent study Baseline to Week 52/EOT in the mean NMPP NRS score;
- Proportion of patients who are better or much better on the PGIC for NMPP at Week 52/EOT;
- Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia NRS scores;
- Proportion of patients who are better or much better on the PGIC for dyspareunia at Week 52/EOT;
- Change from the parent study Baseline to Week 52/EOT in the mean dyspareunia functional impairment on the sB&B scale;
- Change from the parent study Baseline to Week 52/EOT in severity scores on the PGA for pain;
- Proportion of responders at Week 52/EOT based on EHP-30 Pain Domain scores;
- Change from the parent study Baseline to Week 52/EOT in function impairment on the PGA for function;
- Change from the parent study Baseline to Week 52/EOT in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
- Change from the parent study Baseline pain assessment period to Week 52/EOT in dysmenorrhea-related functional effects (sB&B);
- Change from the parent study Baseline pain assessment period to Week 52/EOT in NMPP-related functional effects (sB&B).

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

For endpoint of proportion of responders at Week 52/EOT based on EHP-30 Pain Domain scores, a responder is defined using the same within-patient score change threshold determined from the parent studies.

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.

The treatment-emergent period will be defined as the period of time from the first dose date and time of randomized study drug in the parent study 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, 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, high level term, and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

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

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

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. ECGs will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

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

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

Additional analyses will be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Pharmacodynamics Analyses

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

9.7. Exploratory Analyses

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

- Change from Baseline to Week 52/EOT in the EHP-30 scale total score;
- Change from Baseline to Week 52/EOT in the EHP Work Domain score;
- Change from parent study Baseline to Week 52/EOT in the EQ-5D-5L.

9.8. Interim Analyses

There are no planned interim efficacy analyses.

9.9. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

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

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient 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 lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, accountability, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient 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. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery, and document the deviations appropriately in the study files.

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

10.2.3. 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). 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.

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APPENDICES

Appendix 1. 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).

Appendix 2. Daily eDiary

Version 3 MY80005-eDiary
US English Screen Report 23May2017

Screen report: my80005-eDiary Subject Facing

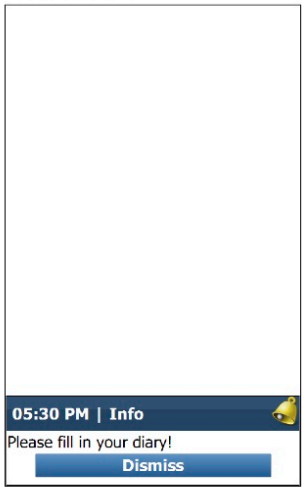
Localized texts are displayed in English.

Contents

Version 3
US English Screen Report

MY80005-eDiary
23May2017

1 Common



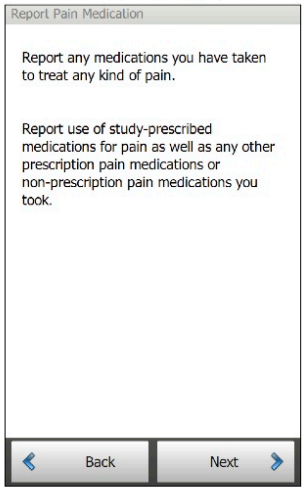
Message 1

Note: Time will populate per device

Version 3
US English Screen Report

MY80005-eDiary
23May2017

2 Form: MedReport



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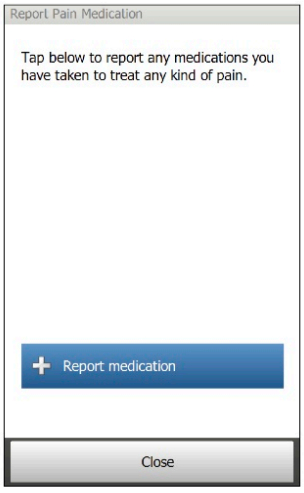

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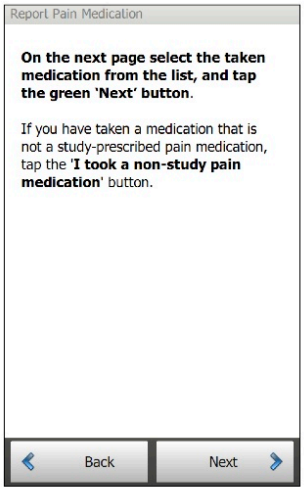

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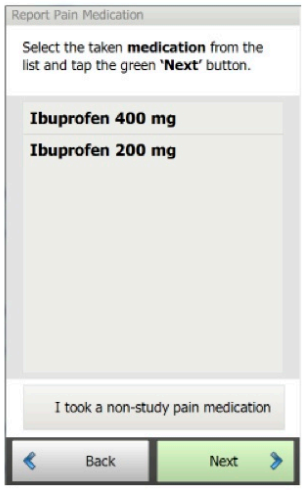


Screen 4

Note: Medications will show per patient set up

Message 1

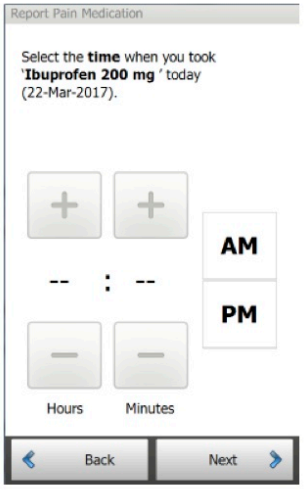
Screen 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2

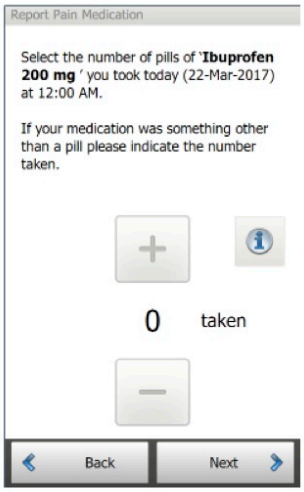


Screen 6

Message 3

Note: Medication Name and Date will show per device

Message 4



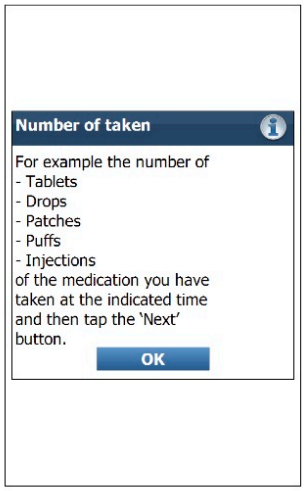
Screen 7

Message 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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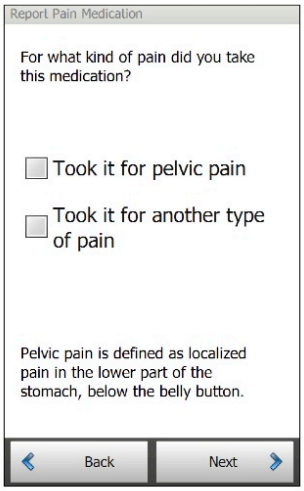

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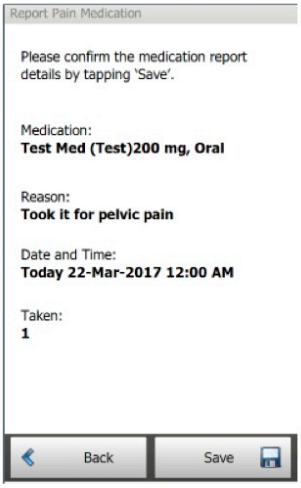
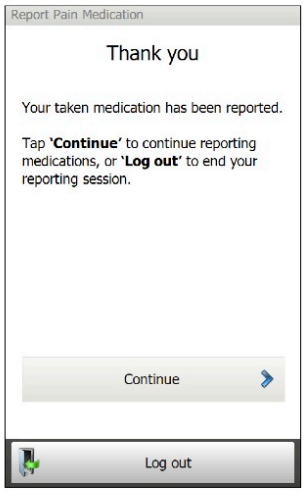


Screen 9

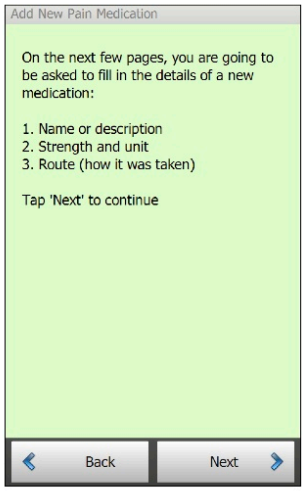
Note: 'Medication', 'Reason', 'Date and Time', 'Taken' will show per patient selection



Screen 10

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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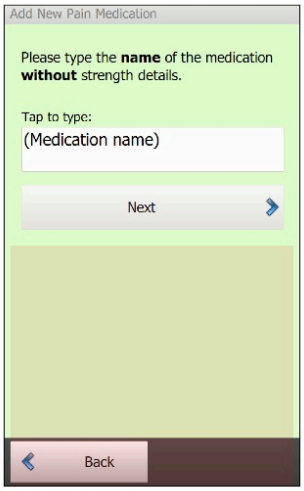
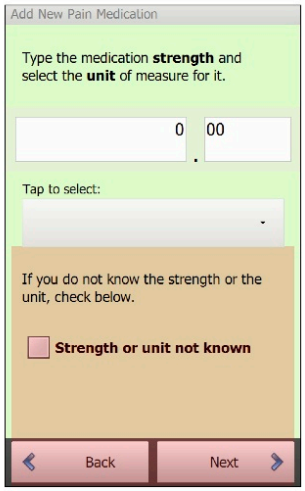


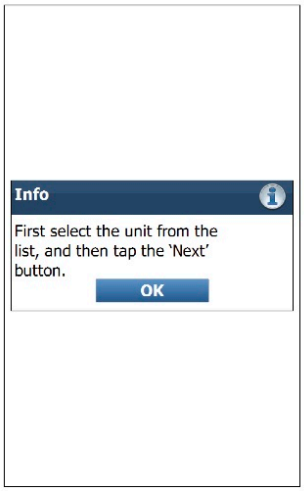
Screen 12

Message 7



Screen 13

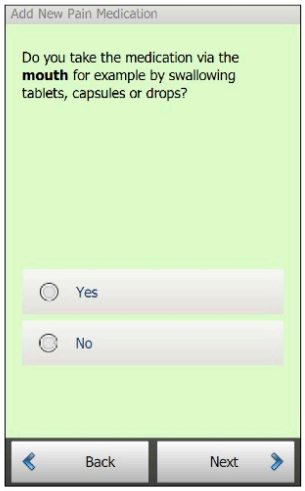
Message 8



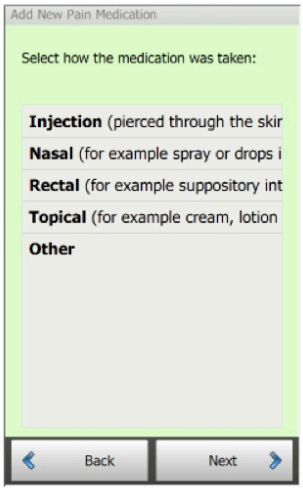
Message 9

Version 3
US English Screen Report

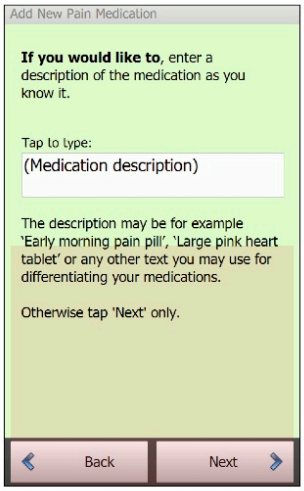
MY80005-eDiary
23May2017



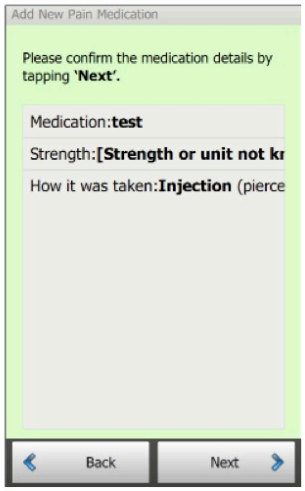
Screen 14



Screen 15



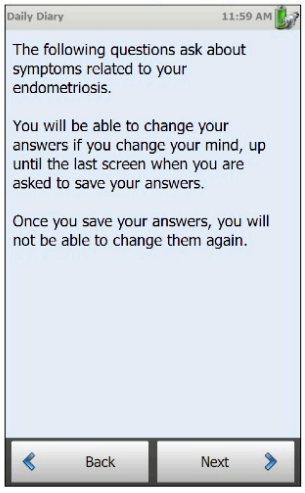
Screen 16



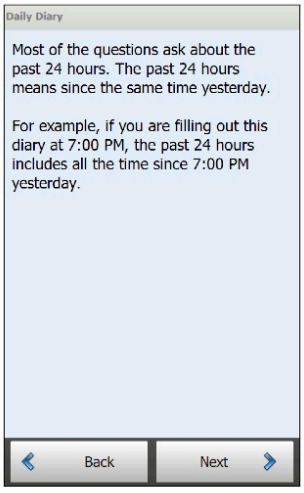
Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

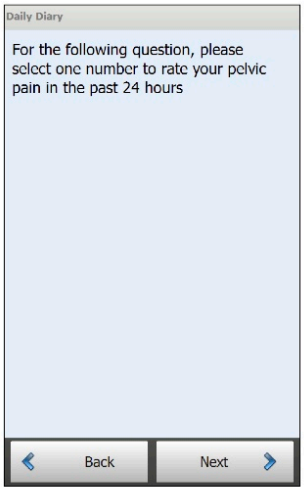
3 Form: Daily Diary



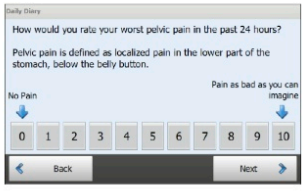
Screen 1



Screen 2

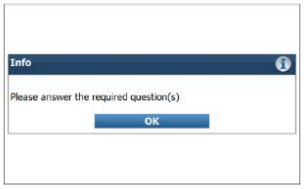


Screen 3



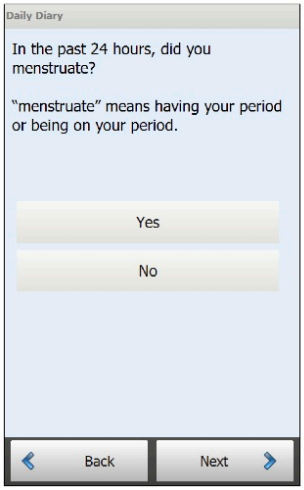
Screen 4

Note: Screen will show latteraly on device



Message 1

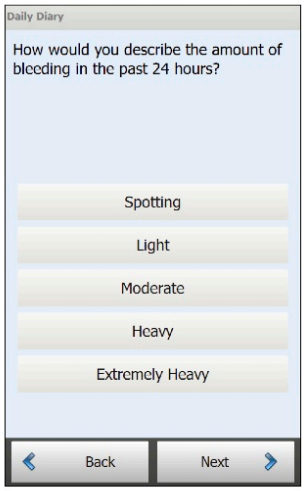
Note: Screen will show latteraly on device



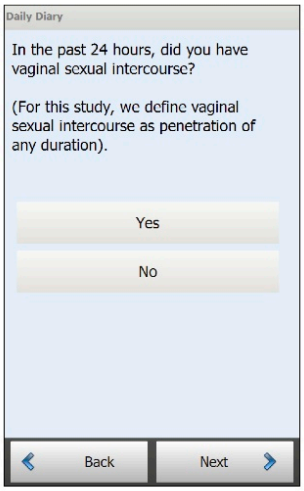
Screen 5

Version 3
US English Screen Report

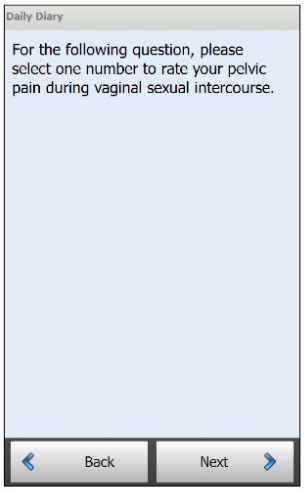
MY80005-eDiary
23May2017



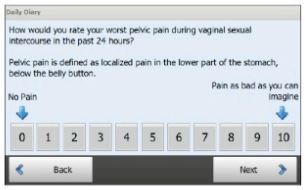
Screen 6



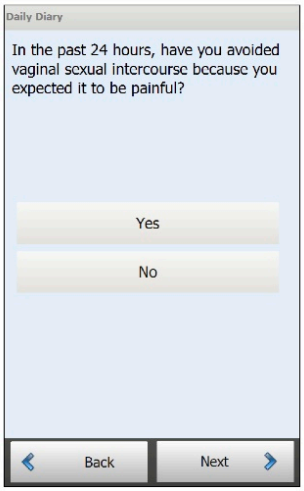
Screen 7



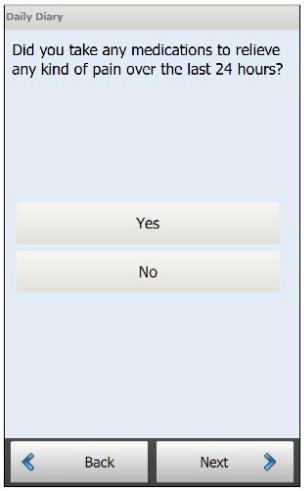
Screen 8



Screen 9



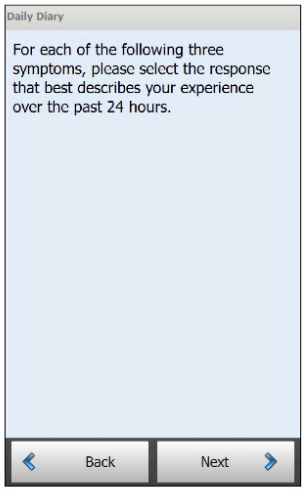
Screen 10



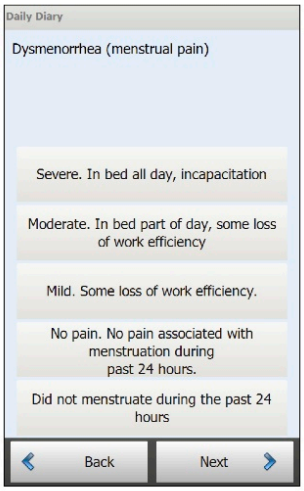
Screen 11

Version 3
US English Screen Report

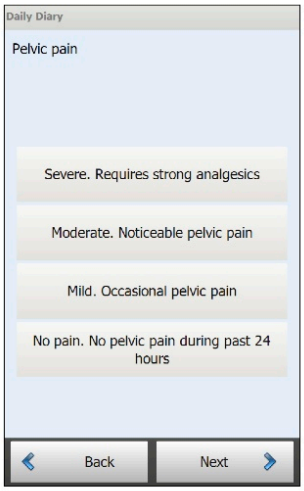
MY80005-eDiary
23May2017



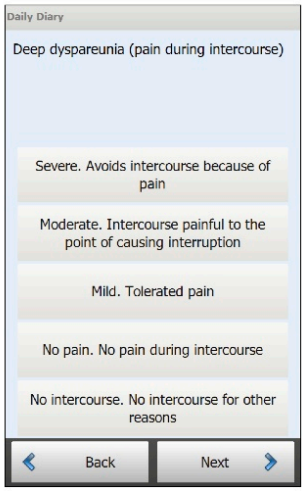
Screen 12



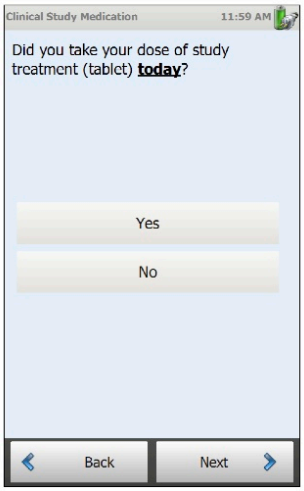
Screen 13



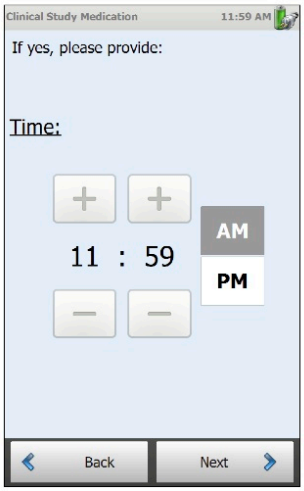
Screen 14



Screen 15



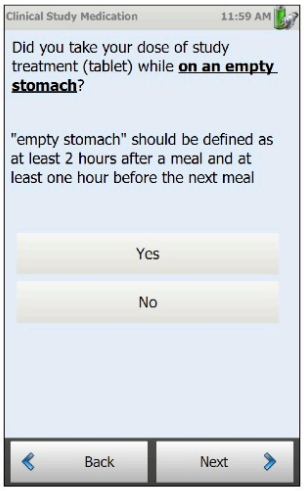
Screen 16



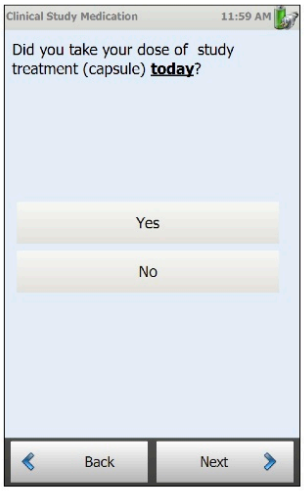
Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

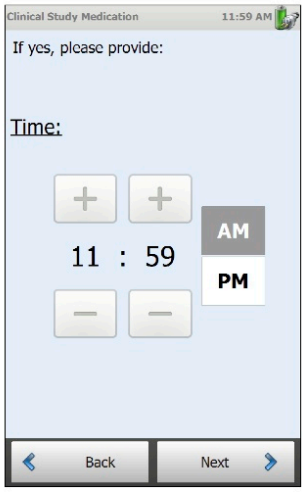
Message 2



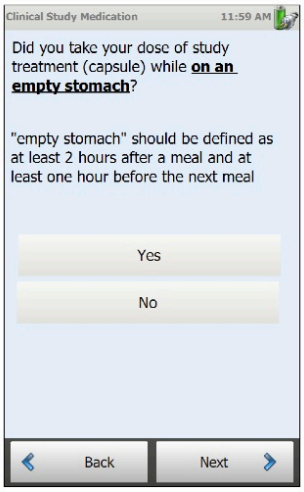
Screen 18



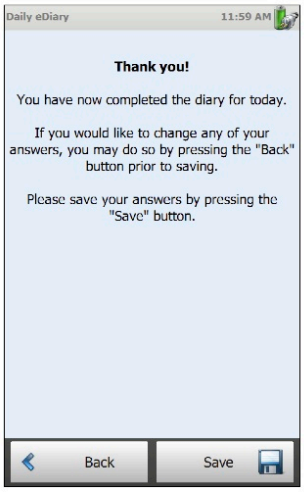
Screen 19



Screen 20



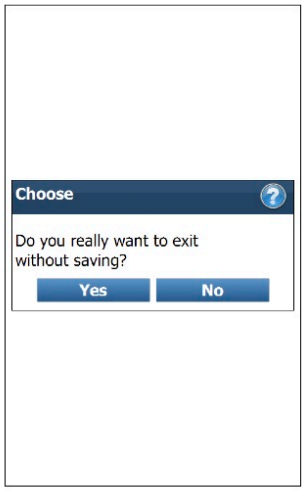
Screen 21



Screen 22

Version 3
US English Screen Report

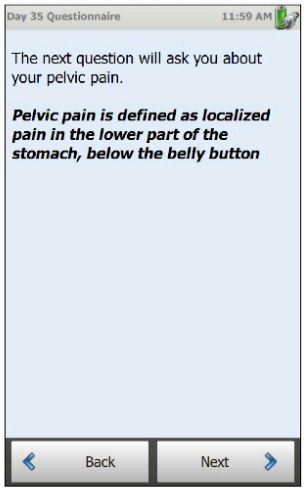
MY80005-eDiary
23May2017



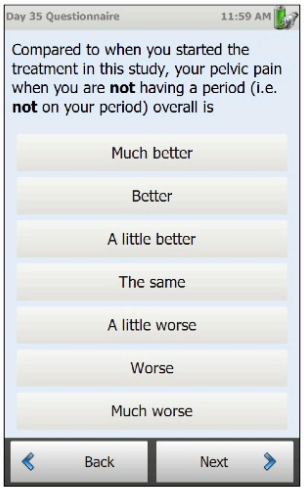
Message 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

4 Form: PGIC-NMPP

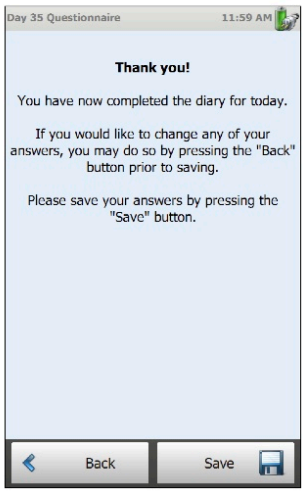


Screen 1



Screen 2

Message 1

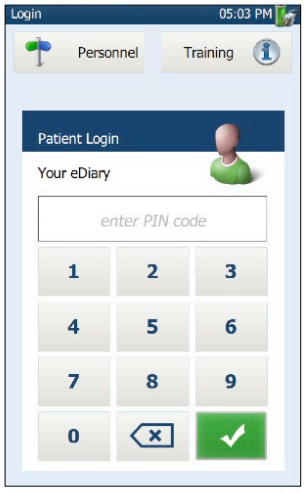


Screen 3

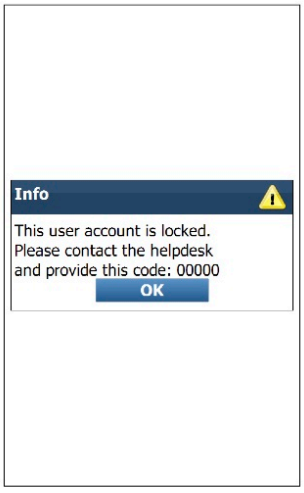
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

5 Form: Login



Screen 1

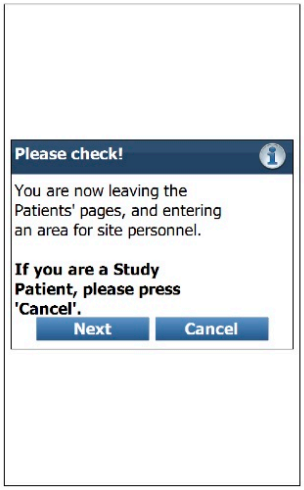


Message 1

Message 2

Message 3

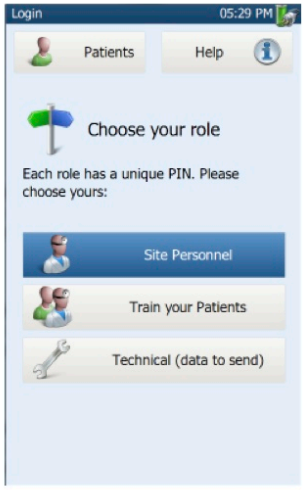
Message 4



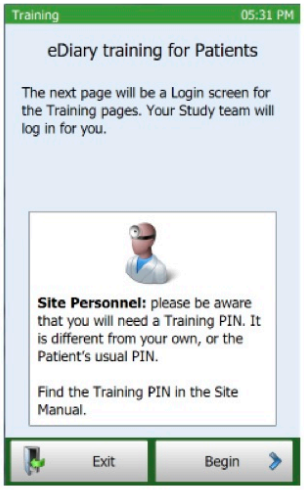
Message 5

Version 3
US English Screen Report

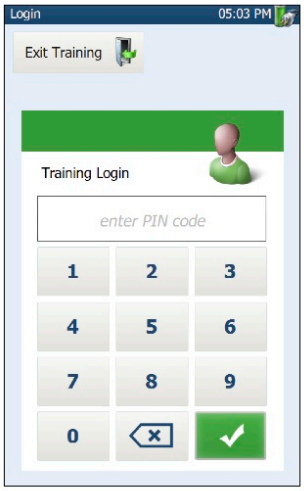
MY80005-eDiary
23May2017



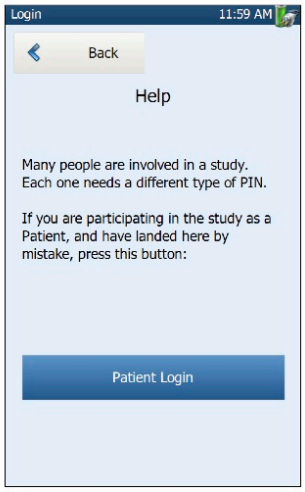
Screen 2



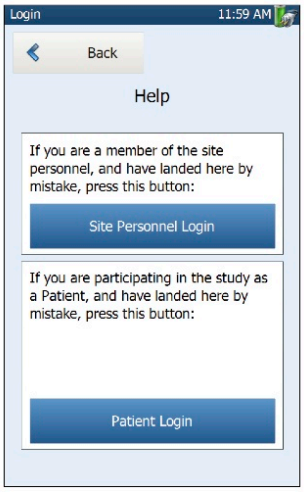
Screen 3



Screen 4



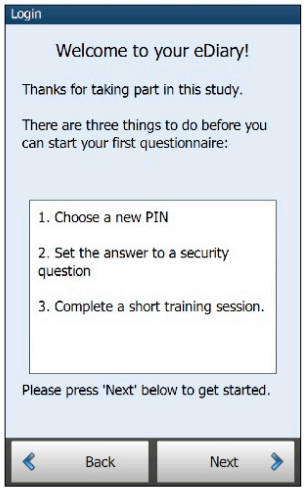
Screen 5



Screen 6

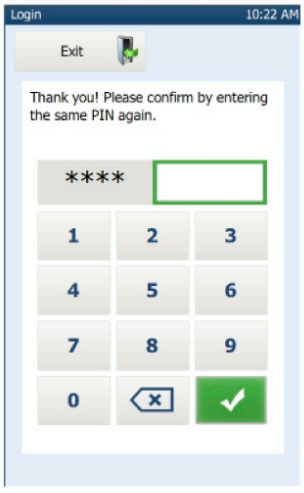
Version 3 MY80005-eDiary
US English Screen Report 23May2017

6 Form: PIN change



Screen 1

Screen 2

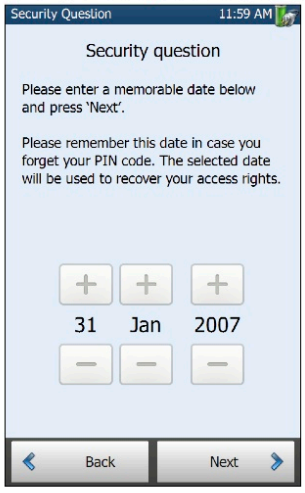


Screen 3

Message 1

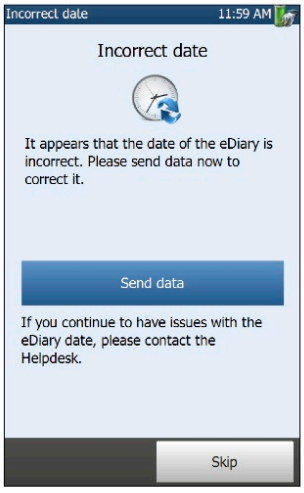
Version 3 MY80005-eDiary
US English Screen Report 23May2017

7 Form: Subject main menu

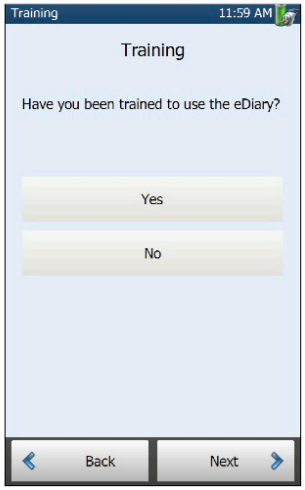


Screen 1

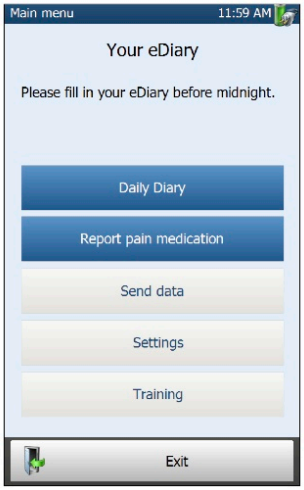
Message 1



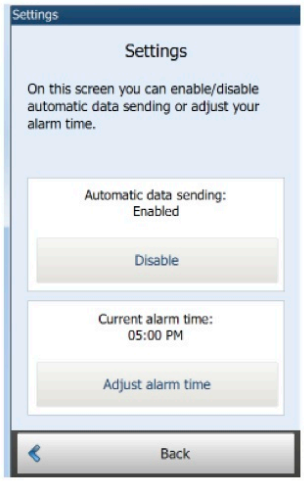
Screen 2



Screen 3



Screen 4



Screen 5

Note: Time will update per device

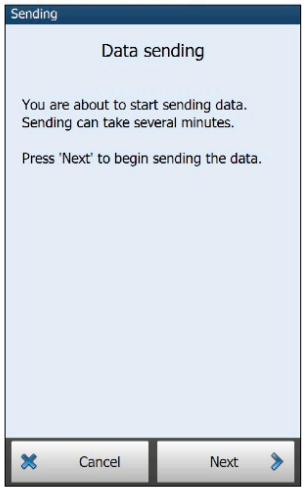
Version 3
US English Screen Report

MY80005-eDiary
23May2017

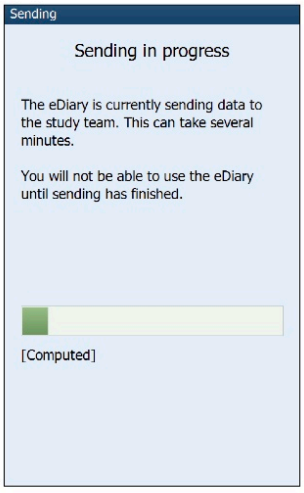
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

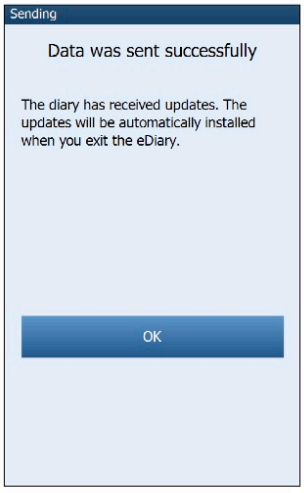
8 Form: Sending



Screen 1



Screen 2



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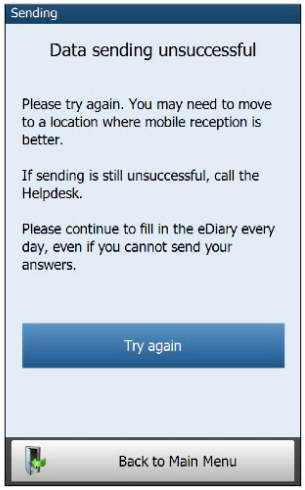

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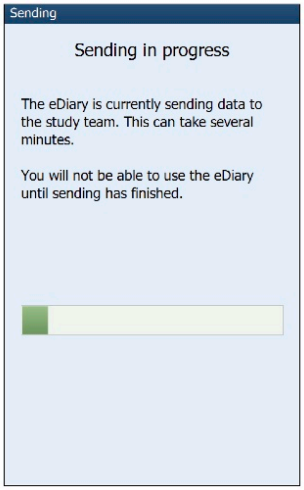
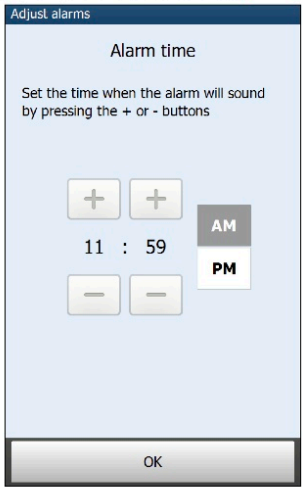


Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017

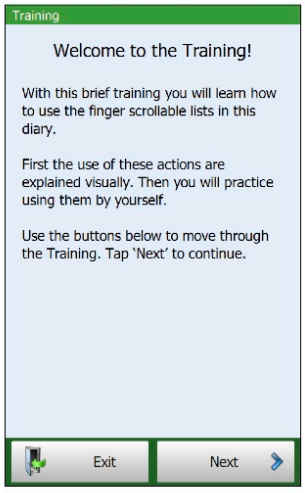
9 Form: AlarmSetup



Screen 1

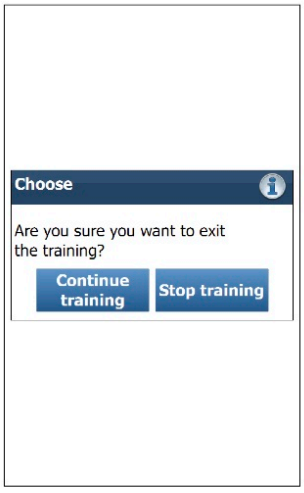
Version 3 MY80005-eDiary
US English Screen Report 23May2017

10 Form: Subject training diary



Screen 1

Message 1



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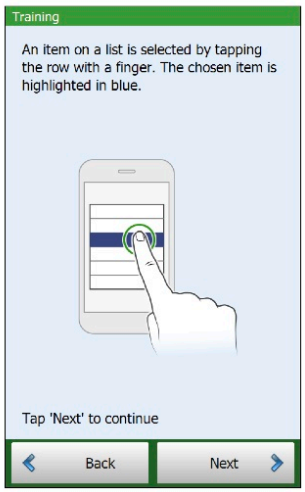

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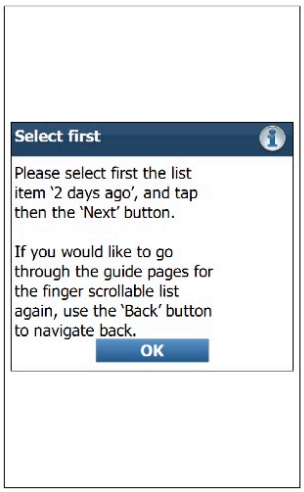
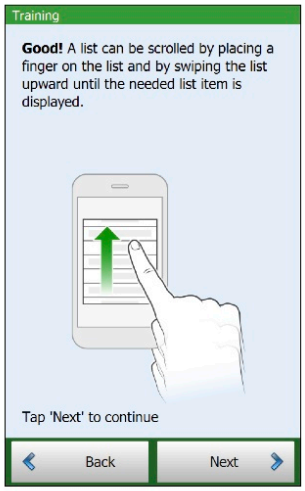
Screen 3



Message 3

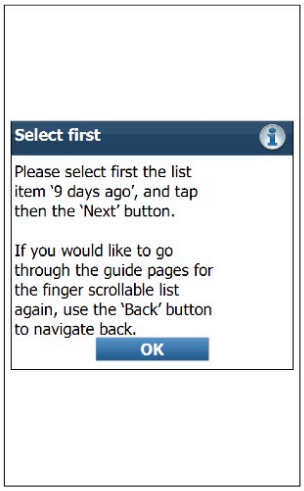
Version 3
US English Screen Report

MY80005-eDiary
23May2017



Screen 4

Screen 5



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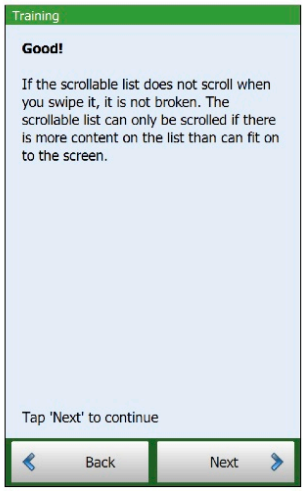

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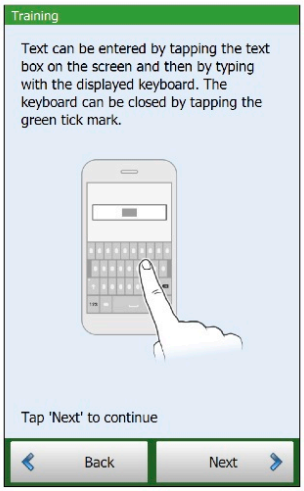

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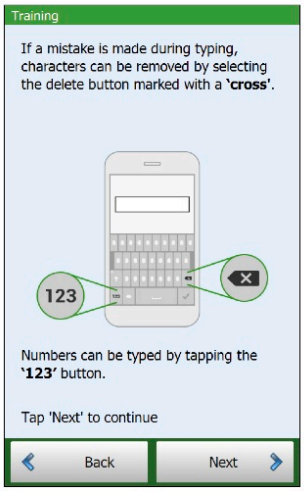
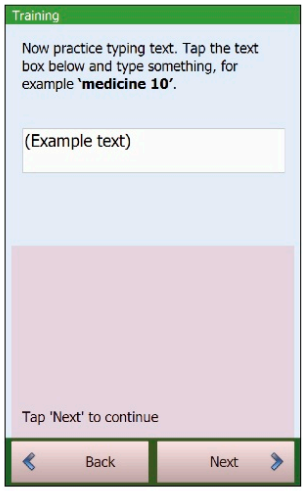


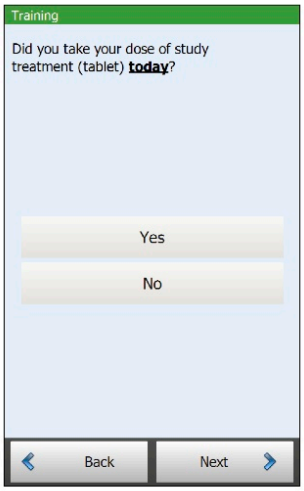
Screen 8

Version 3
US English Screen Report

MY80005-eDiary
23May2017

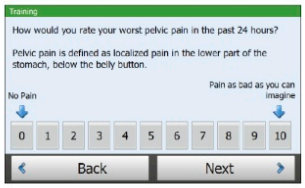


Screen 9



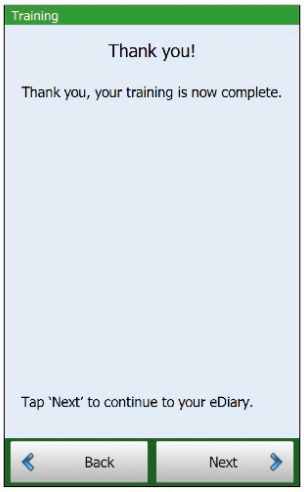
Screen 10

Message 5



Screen 11

Note: Screen will show latteraly on device



Screen 12

Version 3
US English Screen Report

MY80005-eDiary
23May2017

11 Keyboards

Appendix 3. 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 4. 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 ❑

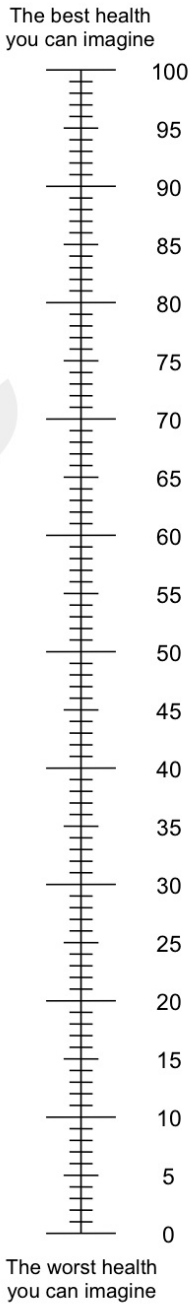
ANXIETY / DEPRESSION

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 5. 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 function)

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

Not at all
Minimally
Moderately
Significantly
Very significantly

Note: PGA for function is administered via a paper questionnaire.

Appendix 6. Endometriosis Health Profile - Work Domain

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.***

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

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:

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

Recommended tests:

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

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

CBC, complete blood count; INR, international normalized ratio.

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

CLINICAL STUDY PROTOCOL

Study Title:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifiers:	IND# 076642 EudraCT # 2017-004066-10
Version and Effective Date:	Original: 06-NOV-2017 Amendment 1: 20-MAR-2018

AMENDMENT 1: SUMMARY OF CHANGES

The main purpose of the amendment was to align the protocols with changes made to the parent protocols MVT-601-3101 and MVT-601-3102 in Amendment 1. A detailed list of changes is described below. Note that corrections of typos, administrative changes, minor clarifications and minor wording changes to improve readability and understanding, and version and signatory updates are not included in this table.

Item; Section(s)	Original	Amendment 1	Rationale
Synopsis: Study Objectives and Endpoints Section 3.0 Section 9.4	N/A	Secondary endpoint responder analyses for EHP-30 pain domain added at Week 52. "Proportion of responders at Week 52/EOT based on their EHP-30 Pain Domain score."	To support the key secondary objective related to function, to define a responder for this endpoint, and to align with Amendment 1 update to the parent studies.
Section 3.0 Section 9.4		For endpoint of proportion of responders at Week 52/EOT based on EHP-30 Pain Domain scores, a responder is defined using the same within-patient score change threshold determined from the parent studies.	
Synopsis: Inclusion and Exclusion Criteria Section 4.3.1	EC #1 "Has had gynecologic surgery or other surgical procedures for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102)."	EC #1 "Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102)."	To simplify wording to improve clarity and to align with Amendment 1 update to the parent studies.
Section 4.6	None	Clarification that "throughout the study" also included the 30 days following the last dose of study drug. ". . . including through 30 days following the	To clarify duration of required contraception to align with

Item; Section(s)	Original	Amendment 1	Rationale
		last dose of study drug"	Amendment 1 update to the parent studies.
Section 1.1 footnotes Section 6.3	The early termination visit DXA is not required if the early termination visit occurred prior to the Week 32 visit.	The early termination visit DXA is not required if the early termination visit occurred prior to the Week 32 visit or within 4 weeks after completion of the Week 36 DXA.	To remove the need to perform a repeat DXA when one was recently performed.
Section 4.5 Section 6.2	None	Procedural details for IVRS/IWRS and e-Diary deactivation added. "When patients complete the study or early terminates from the study, they must be deactivated from the study in the IVRS/IWRS, eDiary, and tablet device."	To facilitate compliance with procedures previously described in other documents (eg, user manuals) only.
Section 5.6	Study drug storage temperatures and excursion ranges stated in the protocol.	Referred reader to study drug labeling for details of study drug storage: Added: "at room temperature. Follow storage conditions described on the drug labeling."	To ensure most current storage information is used and to align with Amendment 1 update to the parent studies.
Section 5.7 Section 5.10.1, footnote 1	None	New section ("Rescue Analgesic Medications") added to describe in additional detail a) analgesic use during washout; b) procedure to follow for patients whose pain is uncontrolled despite use of study-specified analgesics; c) add allowance for short-term use of non-study specified analgesics for treatment of intercurrent events (eg, injury or surgery), if required; d) details on timing of dispensation and prescribing of Tier 1 and Tier 2 analgesics.	To provide further procedural information and to allow short-term non-study specified analgesics for intercurrent events, if needed and to align with Amendment 1 update to the parent studies.
Section 5.9	None	Sites to retain both used and unused drug kits at Week 24/Baseline and at Week 52/ET. At all other visits, only used drug kits should be retained at the site.	To clarify the visits at which unused drug kits should be returned to sites.
Schedule of Activities	None	Order in which paper and electronic tablet questionnaires should be completed during the	To add consistency and to align with

Item; Section(s)	Original	Amendment 1	Rationale
footnotes x and y Section 6.2		visit were specified.	Amendment 1 update to the parent studies.
Synopsis Study Design Schedule of Activities footnote r Section 4.1 Section 6.5.2.6	Follow-up DXA to be done for patients not continuing into the extension if BMD loss is >3% at the Week 52/ET visit.	Follow-up DXA to be done for patients if BMD loss is >3% at the Week 52/ET visit or most recent study scan.	To clarify procedure to be followed for patients who terminated early but did not undergo an ET visit and to align with Amendment 1 update to the parent studies.
Section 7.6	Safety Report Forms to be submitted to PRA Safety & Risk Management	Safety Report Forms to be submitted to IQVIA RDS Inc.	To reflect a change in the safety vendor.
Section 1.o Section 9.2 Section 9.4	ITT analysis	Modified ITT analysis (mITT)	The term “ITT” was updated to “modified ITT” to better reflect that planned analysis The planned analysis was not changed.
Section 5.6 Section 10.1.7	Kit numbers to be maintained during drug accountability	Lot numbers to be maintained during drug accountability.	To reflect the fact that study drug kits contain lot numbers.
Section 10.2.1	None	Statement added that sponsor safety reporting will comply with global regulatory guidance.	To clarify that safety reporting will be in accordance with US and non-US health authority requirements and to align with Amendment 1 update to the parent studies.
Section 10.2.2	None	Statement added that all protocol modifications will be submitted to the appropriate IRB or IEC for information and approval in accordance with local requirements and to the appropriate Health Authority, if required.	To clarify that protocol modifications will be in accordance with US and non-US

Item; Section(s)	Original	Amendment 1	Rationale
			health authority requirements and to align with Amendment 1 update to the parent studies.
Appendix 1	List of Tier 1 and Tier 2 study-specified medications by country	Updated to specify Tier 1 and Tier 2 study-specified analgesic examples and prescribing procedures.	To align with Amendment 1 update to the parent studies.

CLINICAL STUDY PROTOCOL

Study Title:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifiers:	IND No. 076642 EudraCT No. 2017-004066-10
Version and Effective Date:	Original: 06 NOV 2017 Amendment 1: 20 MAR 2018 Amendment 2: 11 Dec 2018

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain

Protocol Number: MVT-601-3103 Amendment 2

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

PPD

PPD

11-Dec-2018
Date

PPD

PPD PPD

11-Dec-2018
Date

PPD

PPD PPD

11 DEC 2018
Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dehydroepiandrosterone
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EHP	Endometriosis Health Profile
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
EU	European Union
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HR	heart rate
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NMPP	nonmenstrual pelvic pain
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PLD	phospholipidosis
QTc	corrected QT (interval)

Term	Explanation
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
sB&B	Subject Modified Biberoglu and Behrman
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
ULN	upper limit of normal
US	United States
W	Week
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Protocol Number	MVT-601-3103
Location	Multinational, including North and South America, Europe, Africa, New Zealand, and Australia
Study Centers	Approximately 320 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with endometriosis-associated pain
Number of Patients Planned	Approximately 800
Study Objectives	In women with endometriosis-associated pain, the study objectives are as follows: <u>Primary Efficacy Objectives</u> To be assessed at Week 52 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. To be assessed at Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.
	<u>Secondary Efficacy Objectives</u> To be assessed at Week 52 and Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: o Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; o Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea; o Patient Global Impression of Change (PGIC) for dysmenorrhea; o Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP;

	○ PGIC for NMPP; ○ Dyspareunia, as measured by the NRS; ○ PGIC for dyspareunia; ○ Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]); ○ 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 EHP-30 Pain Domain; ○ Patient Global Assessment (PGA) for pain; ○ PGA for function; ○ Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains; ○ Dysmenorrhea-related functional effects (sB&B); ○ NMPP-related functional effects (sB&B). <u>Safety Objectives</u> • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: ○ Adverse events; ○ Changes in bone mineral density. <u>Pharmacodynamic Objective</u> • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.
	<u>Exploratory Objective</u> • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).
Study Design The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive open-label oral relugolix 40 mg once daily co-administered with low-dose- estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to	

evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 80 weeks. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).

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

Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed according to the following rules:

- For Early Termination occurring between Week 24 and Week 52:
  - For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event.

    Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.
  - For Early Termination occurring after Week 36, DXA is required at Early Termination unless a

DXA result is available from within six weeks prior to Early Termination.

Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline.

Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.

- For Early Termination occurring between Week 52 and Week 104:
  - DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.
  - Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (±1) months and status of menstruation recovery, may be waived.

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.
3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable non-hormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified non-hormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;

b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
c. Has a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted above;
e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study.

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;
6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN); or

b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome); 10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug; 11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor): a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or b. The presenting visual acuity score has decreased by ten or more points at the Week 24/Baseline visit relative to the parent study Baseline visit; Note: Visual acuity score must have been obtained with corrective lenses, if applicable. 12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor; 13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).	
Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 80 weeks (Open-Label Treatment Period). Concomitant Medicinal Products Systematically Prescribed for All Study Patients Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug and a second-line opioid or opioid/acetaminophen or opioid/paracetamol combination for endometriosis-related pain relief as required. The specific analgesic drugs offered may differ for different countries or regions. The analgesics for each patient will be the same as those prescribed for her during the parent study.
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and Week 52, and between the parent study Baseline and the end of the extension study (Week 104) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will

	establish the patient's baseline for both the parent study and the extension study. Primary Efficacy Endpoints Week 52 • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. Week 104 • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores. Secondary Efficacy Endpoints To be assessed at Week 52 and Week 104, unless otherwise specified • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea (at Week 52 only); • Change from the parent study Baseline in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP (at Week 52 only); • Change from the parent study Baseline in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only);; • Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline in severity scores on the PGA for pain; • Proportion of responders based on their EHP-30 Pain Domain score; • Change from the parent study Baseline in function impairment on the PGA for function; • Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B). Safety Endpoints

	To be assessed at Week 52 and Week 104 • Incidence of adverse events; • Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. Pharmacodynamic Endpoint To be assessed at Week 52 and Week 104 • Change from parent study Baseline in predose concentrations of serum estradiol. Exploratory Endpoints To be assessed at Week 52 and Week 104 • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.

Statistical Methods

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

There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.

Efficacy

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

The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

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

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52 or Week 104).

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, high level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values will be classified by toxicity grade based on the National Cancer Institute CTCAE. Laboratory shift tables of the parent study Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits. The

absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change from parent study Baseline to Week 52 in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant. The 95% CI for mean percentage change at Week 104 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104 as supportive analyses.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3101 or MVT-601-3102) and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3103

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week 44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Informed Consent	X[d]											
Review Eligibility Criteria	X											
Concomitant Medications[e]	X[f]	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Weight	X[g]		X			X		X		X	X[h]	
Complete Physical Examination	X[g]					X[i]				X[i]	X[h]	
Visual Acuity[j]	X[g]											
Signs and Symptoms-Directed Physical Examination[k]		X	X	X	X		X	X	X		X[h]	X
12-Lead ECG[l]	X[g]					X					X[h]	
Clinical Laboratory Tests[m]	X[g,n]	X	X	X	X	X[n]	X	X	X	X[n]	X[h]	X
Pharmacodynamics Sample[o]	X[g,n]					X[n]				X[n]	X[h,n]	

	PERIOD										SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week 44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Urinalysis	X[g]					X				X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Daily eDiary[p]	X[g]	X	X	X	X	X	X	X	X	X		X
Site Review of eDiary Data	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Bone Densitometry[q]	X[g]		X			X[r,s]				X[r,s]	X[h]	
Endometrial Biopsy	X[g,t]					X				X[t]	X[h]	
Dispense Study Treatment	X	X	X	X	X	X	X	X	X		X[h]	
Dispense or Prescribe Protocol-Specified Analgesic Drugs[u]	X	X	X	X	X	X	X	X	X		X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic	X[v]					X				X	X[h]	
Daily Self-Administration of Study Treatment[w]		X ---------- X										
Take Protocol-Specified Rescue Analgesics as Needed[x]		X ---------- X										
EHP-30 Questionnaire[y]	X[g]		X		X	X		X		X	X[h]	

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week 44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Patient Global Assessment for Pain[y]	X[g]	X	X	X	X	X	X	X	X	X	X[h]	
[on paper] Patient Global Assessment for Function[z]	X[g]	X	X	X	X	X	X	X	X[n]	X	X[h]	
Patient Global Impression of Change[y]	X[g]		X			X					X[h]	
[on paper] EHP Work Domain[z]	X[g]					X		X		X	X[h]	
EQ-5D-5L Questionnaire[y]	X[g]					X		X		X	X[h]	
Adverse Event Collection[aa]	X	X	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery												X[bb]
Telephone Contact[cc]						X (W57)	X (W71)	X (W85)	X (W98)			

BP = blood pressure; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; eDiary = electronic diary; EHP = Endometriosis Health Profile; EQ-5D-5L = European Quality of Life Five-Dimension Five-Level Scale; HR = heart rate; NRS = Numerical Rating Scale; PGA = Patient Global Assessment; sB&B = Subject Modified Biberoglu and Behrman; W = week.

[a] The Week 52 visit should occur on or after the 1-year anniversary of Baseline Day 1 of the parent study, and the Week 104 visit should occur on or after the 2-year anniversary of Baseline Day 1 of the parent study.

[b] Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.

[c] The Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit.

[d] May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3103 is defined by administration of the first dose of MVT-601-3103 study drug.

[e] Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up Period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3103 should be reported as concomitant medications in the parent study

(MVT-601-3101 or MVT-601-3102). If concomitant medication is ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.

[f] Concomitant medications are recorded both for the parent study and for MVT-601-3103 at the Week 24/Baseline visit. (See footnote e for further details).

[g] This is a parent study (MVT-601-3101 or MVT-601-3102) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3103 and is covered under the informed consent for the parent study.

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

[i] The Week 52 and Week 104 physical examinations will include a breast examination.

[j] See parent study protocols (MVT-601-3101 or MVT-601-3102) for instructions on testing visual acuity.

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

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

[m] Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, Week 91, and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests will include the following: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.

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

[o] For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week 104/Early Termination, collect a sample for analysis of estradiol concentrations only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are collected.

[p] All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study. 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 until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.

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

r This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within 4 weeks after completion of the Wek 36 or Week 52 scan. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.

[s] Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed based on the timing of the Early Termination visit. For Early Termination occurring after Week 24 and before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event, and follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. For Early Termination occurring after Week 36 and before Week 52, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2% or most recent DXA result was after Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. For Early Termination occurring between Week 52 and Week 104, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.

[t] Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details), at Week 52 for all patients. All patients are eligible for a biopsy at Week 104; however, patients will have the option to opt out.

[u] Please see Appendix 1 for list of protocol-specified analgesics and see the Investigator Site File for information on where and how to obtain protocol-specified analgesic medications by country. At the Week 104 visit, patients who will not be proceeding to another 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 another extension study, refer to the protocol for that next study.

[v] Pregnancy test must be negative before the study drug dose is administered. For patients whose Baseline Day 1 visit is conducted on a different day than the parent study Week 24 visit, perform an unscheduled pregnancy test at Baseline Day 1 prior to administering the first dose of study drug.

[w] Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week 104/Early Termination visit.

[x] Patients may only take their study-specified analgesics for pain. Analgesics should not be taken prophylactically (ie, in anticipation of pain).

[y] The patient will enter her response(s) into an electronic 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.

[z] The patient will enter her response onto a paper questionnaire at the site. Paper questionnaires should be done in the following order: PGA for function, EHP Work Domain.

[aa] Collect adverse events from the time that the first dose of study drug for MVT-601-3103 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3103 should be reported as an adverse event in the parent study (MVT-601-3101 or MVT-601-3102). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.

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

[cc] A telephone call will be performed at Weeks 57, 71, 85, and 98. The following activities should be completed: a concomitant medication review, evaluation of adverse events, a reminder of compliance with non-hormonal contraception requirements and the need to call the investigator if pregnancy is suspected, and a review of eDiary and study medication compliance.

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 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-oophorectomy 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

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

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once-daily oral medication for the treatment of 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 was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

3. STUDY OBJECTIVES AND ENDPOINTS

Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and Week 52, and between the parent study Baseline the end of the extension study (Week 104) for the following parent study treatment groups:

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

The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study.

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

Objectives	Endpoints
Primary Efficacy	
To be assessed at Week 52 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. To be assessed at Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	To be assessed at Week 52 • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. To be assessed at Week 104 • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores.
Secondary Efficacy	
To be assessed at Week 52 and Week 104 To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: • Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; • Dysmenorrhea, as measured by the NRS for dysmenorrhea; • Patient Global Impression of Change (PGIC) for dysmenorrhea; • NMPP, as measured by the NRS for NMPP;	To be assessed at Week 52 and Week 104, unless otherwise specified • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea (at Week 52 only); • Change from the parent study Baseline in the mean NMPP NRS score;

Objectives	Endpoints
• PGIC for NMPP;	• Proportion of patients who are better or much better on the PGIC for NMPP (at Week 52 only);
• Dyspareunia, as measured by the NRS;	• Change from the parent study Baseline in the mean dyspareunia NRS scores;
• PGIC for dyspareunia;	• Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only);
• Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]);	• Change from the parent study Baseline 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 function measured by the EHP-30 Pain Domain;	• Proportion of responders based on EHP-30 Pain Domain scores;
• Patient Global Assessment (PGA) for pain;	• Change from the parent study Baseline in severity scores on the PGA for pain;
• PGA for function;	• Change from the parent study Baseline in function impairment on the PGA for function;
• Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains;	• Change from the parent study in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
• Dysmenorrhea-related functional effects (sB&B);	• Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B);
• NMPP-related functional effects (sB&B).	• Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).
Safety	
To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	To be assessed at Week 52 and Week 104
• Adverse events;	• Incidence of adverse events;
• Changes in bone mineral density.	• Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).

Objectives	Endpoints
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	To be assessed at Week 52 and Week 104 • Change from parent study Baseline in predose concentrations of serum estradiol.
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	To be assessed at Week 52 and Week 104 • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive open-label oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 80 weeks. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open-label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed

during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

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

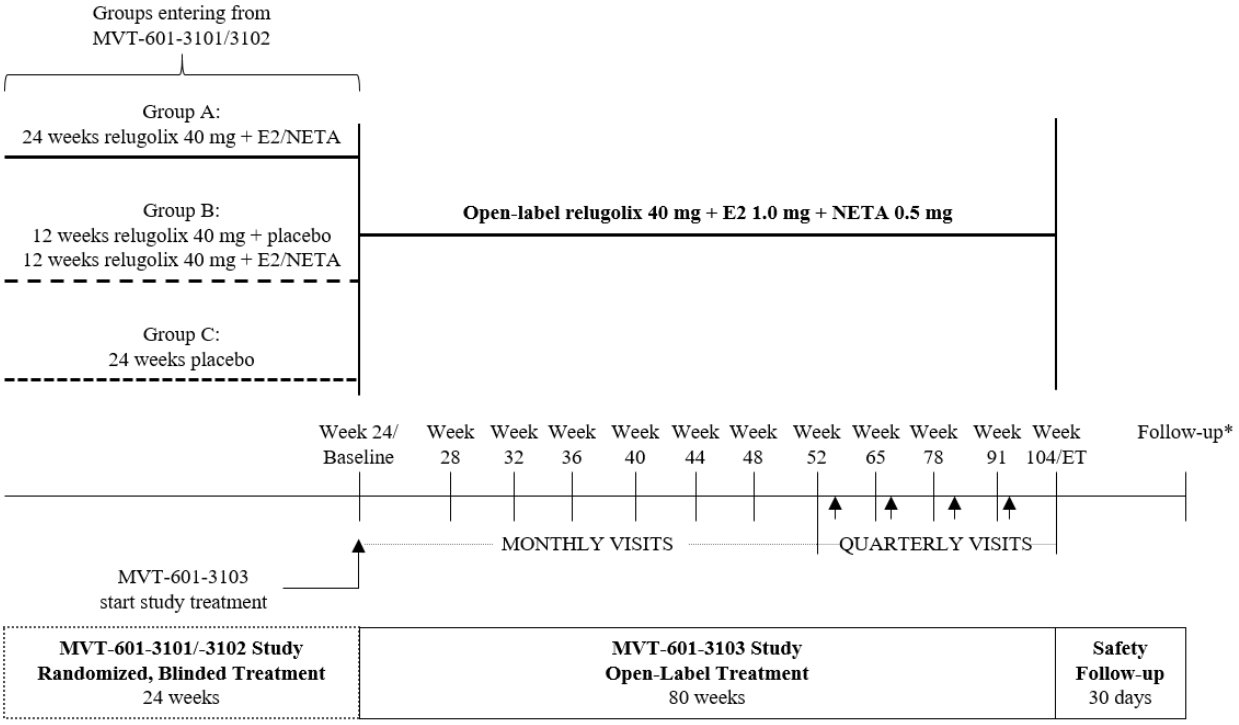
At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via DXA. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, may be waived.

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

Figure 1-1 MVT-601-3103 Study Schematic



E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; eDiary = electronic diary; ET = Early Termination.
* The Follow-up visit is schedule approximately 30 days after the last dose of study drug.
↑ Indicates telephone contact to review concomitant medication, evaluation of adverse events, and a review of eDiary and study medication compliance. To be conducted at Week 57, Week 71, Week 85, and Week 98.

4.2. Discussion of Study Design, Including Dosing

The SPIRIT EXTENSION study (MVT-601-3103) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3101 and MVT-601-3102) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with endometriosis-associated pain. This 80-week extension study provides additional efficacy and safety data up to 104 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of

the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40-mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 104 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 104 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2017; Lee, 2016; Franke, 2000] or endometriosis-associated pain [Wu, 2014]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the United States (US) as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that

lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3101 and MVT-601-3102) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a significant decrease in endometriosis-associated pain in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose estradiol and norethindrone acetate to decrease dysmenorrhea and NMPP and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 80 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102). This study design will allow eligible patients with endometriosis-associated pain, including those randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 800 premenopausal women aged 18 to 51 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. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.

3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable non-hormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified non-hormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;

6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or
    b. The presenting visual acuity score has decreased by ten or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.

12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor;
13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).

4.4. Method of Assigning Patients to Treatment Group and Patient Identification Number

Eligible patients who sign consent will be identified with the same Patient Identification (ID) Number assigned to the patient during the parent study. This extension study is a single-arm, open-label study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).

4.5. Removal of Patients from Therapy

Completion of the Week 104 visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 104 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication). When patients complete the study or early terminate from the study, they must be deactivated from the study in the interactive voice response system/interactive web response system (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 enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 x ULN; or
  - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);

- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. Gross noncompliance includes < 75% compliance with the study drug over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive months) noncompliance (< 50% of the required number of days) with eDiary completion up to Week 52 or persistent (≥ 2 eDiary collection cycles) noncompliance (< 50% of the required number of days) with eDiary completion from Week 52 to Week 104. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting).

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

4.6. Contraception/Pregnancy Avoidance

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

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure) at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
- Has a non-hormonal intrauterine device (eg, Paragard) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described below;

- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

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

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

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

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

Urine pregnancy tests will be performed according to the Schedule of Activities (Table 1-1; including just prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients should call the investigator immediately if they suspect they may be pregnant. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

5. TREATMENTS

5.1. Treatments Administered

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

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

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

Table 1-2 Description of MVT-601-3003 Study Drugs

Name of Investigational Product	Relugolix	Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material
Dosage Form	Tablet	Capsule
Unit Dose Strength	40 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily/ 80 weeks	Oral once daily/ 80 weeks

Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug (NSAID) and a second-line opioid or opioid/acetaminophen (or paracetamol) 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 1. 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 common excipients.

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

5.3. Randomization and Stratification

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

5.4. Directions for Administration

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

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

On Week 24/Baseline 1, Week 52, and Week 104 clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. 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. Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Investigator Site File. 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 lot/batch 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 and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the Investigator Site File.

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. The study-specified pain medications for each patient will be the same as for the parent study. Only study-specific Tier 1 and Tier 2 analgesic medications (see Appendix 1) should be taken starting with the Baseline/Week 24 visit and subsequently. Analgesic medications will be taken for control of pain and not prophylactically.

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 when appropriate.

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 at the time of enrollment into this study. 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 the time of enrollment in this study, 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.

5.8. Blinding

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

5.9. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and should bring all unused and used (including partially used) study drug kits to each study visit. At the Week 24/Baseline visit and Week 104/Early Termination visit, all used, partially used, and unused study drug kits should be retained at the site. At all other visits, only fully used study drug kits should be retained at the site. New study drug should be dispensed as described in Section 1.1 (Schedule of Activities).

Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Because of the importance to both safety and efficacy evaluation, patients who are grossly noncompliant with eDiary completion must undergo an Unscheduled visit to evaluate reasons for noncompliance 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 4.5 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. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 1-3 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 1-3 are prohibited at any time during the study through the Follow-Up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 1-3 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	
GnRH analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-androgens	danazol	

Drug Class	Examples	Comments
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	Note: All other anticonvulsants are allowed
Aromatase inhibitors	anastrozole letrozole	
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective estrogen receptor modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective progesterone receptor modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine devices	levonorgestrel copper	
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.

Drug Class	Examples	Comments
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.
P-glycoprotein inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir[f]	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.
Moderate and strong P-glycoprotein- inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	Note: For patients requiring a short course of these drugs during the study, investigator must contact the medical monitor for approval and guidance on study drug administration during this period.

Drug Class	Examples	Comments
Analgesic drugs **other** than those specified for use during the study[h]	Acetaminophen/paracetamol (other than any included in a study-specified analgesic) aspirin > 325 mg/day NSAIDs (other than study-specified NSAIDs) gabapentin pregabalin carbamazepine metamizole cannabinoids	Note: Aspirin ≤ 325 mg per day is allowed
Antidepressants New treatment or changed doses of SSRI, SNRI, or TCA antidepressants	**SNRI examples:** duloxetine venlafaxine desvenlafaxine **SSRI examples:** citalopram fluoxetine paroxetine fluvoxamine **TCA examples:** amitriptyline doxepin desipramine nortriptyline	SSRI, SNRI, or TCA allowed if given at the same dose as used during the 3 months prior to the Run-In Period of MVT-601-3101 or MVT-601-3102. 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.

DHEA = dihydroepiandrosterone; GnRH = gonadotropin-releasing hormone; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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.
h. For situations where non-study analgesics may be allowed, see Section 5.7.

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded in the electronic Case Report Forms (eCRFs), including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

All analgesics will be collected in the eDiary and recorded in the eCRFs.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of endometriosis is prohibited from the Week 24/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 2 periods: Open-Label Treatment Period and Safety Follow-Up Period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3101 or MVT-601-3102 will serve as the Week 24/Baseline procedures for patients who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

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

- Informed consent (unless signed previously);
- Record concomitant medications;
- Update the patient's status in the IVRS/IWRS as being in the MVT-601-3103 and receive the lot numbers for study drug allocation;
- Dispense study treatment;
- Dispense or prescribe protocol-specified analgesic drugs;
- Transition the patient within her eDiary from the parent study to MVT-601-3103
- Take study drug dose in clinic; and
- Record adverse events, if any.

The Week 24 visit date in the parent study is defined as the date that the last procedures for the Week 24 visit were completed, acknowledging that the Week 24 visit procedures may be completed on different dates. Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. If

necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.).

Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed until Week 52. After Week 52, the eDiary will be collected on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, 52, 65, 78, 91, and 104. Sites will monitor diary completion using the Trial Manager web portal throughout the study.

A telephone call will be performed at Weeks 57, 71, 85 and 98. The following activities should be completed: a concomitant medication review, an evaluation of adverse events, a review of study medication compliance, a reminder of compliance with non-hormonal contraception requirements and the need to call the investigator if pregnancy is suspected, and a reminder to the patient to start recording in the eDiary daily.

Accountability for study drug will be performed at each visit. Instructions for analgesic medication usage will be reinforced at each visit.

Questionnaires are administered on the electronic tablet and on paper at each visit. These procedures should occur before any other types of study procedures are performed. When both electronic tablet and paper questionnaires are required at a visit, 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 function
  - EHP Work Domain [Week24/Baseline, Week 52, Week 78, and Week 104 only]

Patients will bring their eDiary, analgesic medications, and study drug to each visit. The site must document the start and stop dates of the patient's menses.

An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details), at Week 52 for all subjects. All patients will be eligible for the Week 104 biopsy; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78 and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.

Electrocardiograms will be performed at the Week 24/Baseline and the Week 52 visits.

Bone densitometry will occur at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.

Bone densitometry and ECGs will be submitted for central reading.

Study drug compliance will be reviewed at each visit. Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

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

6.3. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. Bone densitometry may be performed at the investigator's discretion, if it aids in follow-up of an ongoing adverse event(s). Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in 6.5.2.6.

Patients (including those who complete the Week 104 visit and those who withdraw early from this study) will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week 104 visit, the Follow-up visit may be waived.

The Follow-up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (see Section 1.1) for individual study visit procedures during the Follow-up visit.

Follow-up of bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.

6.4. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance and

dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Pharmacodynamics Sample Collection

A blood sample for the pharmacodynamic analysis of serum estradiol will be collected predose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week 104 or the Early Termination visit, when no dose is administered. These pharmacodynamic samples will be analyzed at a central laboratory. These results will not be shared with the sites at any time.

6.5.1.2. Patient eDiary

All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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 until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.

The site should review the eDiary data at every visit.

6.5.1.3. 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 3). Patients will complete the EHP-30 questionnaire at the site at visits indicated in Section 1.1 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.

6.5.1.4. 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 4). 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 visits indicated in Section 1.1 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.

6.5.1.5. 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 5) 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. The PGA for pain severity and the PGIC will be completed on a tablet device at the study site. The PGA for function will be completed on a paper questionnaire at the study site.

6.5.1.6. 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 6). Patients will complete the EHP Work Domain questionnaire at visits indicated in Section 1.1 before other types of study procedures, such as blood draws and physical examinations, are performed. The EHP Work Domain will be completed on a paper questionnaire at the study site.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

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

6.5.2.2. Vital Signs

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

6.5.2.3. Physical Examinations

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. The physical examinations at Week 52 and Week 104 will include a breast examination.

6.5.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Investigator Site File 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 1-4.

Table 1-4 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
Creatine kinase		Urine microscopy (reflex testing based on abnormal urine analysis)
Hemoglobin A1c		
Bilirubin total		
Alanine aminotransferase		
Aspartate aminotransferase		
Gamma-glutamyl transferase		
Alkaline phosphatase		
Hormones	**Lipids**	**Pregnancy**
Estradiol	Total cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, 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.

6.5.2.5. Electrocardiograms

Electrocardiograms (12-lead) will be obtained at the time points described in the Schedule of Activities (Section 1.1). Electrocardiograms will be measured using standardized equipment provided by the central core laboratory with the patient in a semi-supine or supine position after

5 minutes of rest. The ECGs will be assessed by central review and a report provided to the site. The investigator or sub-investigator (or a qualified individual at the investigational site) will interpret the ECG report provided by the central reviewer using one of the following categories: normal or abnormal. The investigator or sub-investigator will judge if any of the findings are clinically significant.

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3, and L4), total hip, and femoral neck (same leg within each patient) at the time points described in the Schedule of Activities (Section 1.1). The scans will be read by the central imaging laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will used at each site and operated in the same scan mode for all scans for an individual patient and should be the same as used for the patient during the parent study (MVT-601-3101 and MVT-601-3102). The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study.

Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed according to the following rules:

- For Early Termination occurring between Week 24 and Week 52:
  - For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event.

    Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.
  - For Early Termination occurring after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.

    Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline.

    Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.
- For Early Termination occurring between Week 52 and Week 104:
  - DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.

- Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.

The follow-up bone densitometry will be submitted for central reading.

Patients who experience a bone mineral density loss from the parent study Baseline of ≥ 7% at any of the anatomical sites assessed will be discontinued from the extension study and will undergo another bone densitometry scan as described above. Patients should be assessed for secondary causes of bone loss and followed up further if not improving on the 6-month follow-up scan, unless an alternative etiology has been identified.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the follow-up bone densitometry scan at 6 (±1) months conducted under this protocol may be waived.

6.5.2.1. Endometrial Biopsy

For patients in parent study MVT-601-3101, an endometrial biopsy is performed at the Week 24 visit. If the required Week 24 biopsy is inadequate for diagnosis, it should be repeated, and a sample submitted to the central laboratory. If the second sample is inadequate, ensure an endometrial thickness has been reported from the Week 24 transvaginal ultrasound and contact the medical monitor to review the findings. Patients who have endometrial hyperplasia or endometrial carcinoma will be withdrawn from study drug treatment and followed per instructions in the parent study protocol.

Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 for all patients. At Week 104, all patients will be eligible for an additional endometrial biopsy; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

The Week 52 and Week 104 endometrial biopsy samples will be submitted to the central laboratory. If the Week 52 or Week 104 biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:

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

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

6.5.2.2. Status of Menstruation Recovery

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

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

7. SAFETY CONSIDERATIONS

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

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 admitted to a hospital, independent of the duration of that hospitalization. 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 and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor if the investigator assesses the event as related to the study drug treatment.

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

7.3. Assigning Causal Relationship to Study Drug

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

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

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

CTCAE = Common Terminology Criteria for Adverse Events.

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

7.5. Adverse Events of Clinical Interest Reporting

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

Any ALT or AST elevation of this degree or greater occurring during the Open-Label Treatment Period or 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 serious adverse event criteria**. Additional instructions for evaluating patients with an increase in ALT or AST ≥ 3 x ULN may be found in Appendix 7.

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

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

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

- ALT or AST > 8 x ULN; or
- ALT or AST > 5 x ULN and persists for more than 2 weeks; or
- ALT or AST > 3 x ULN **and** total bilirubin > 2 x ULN **or** the 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-601-3103);
- 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.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy 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 form, as available.

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

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

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on 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 (corrected QT [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD), reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

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

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the parent studies.	Bone mineral density will be monitored at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the parent studies.	12-lead ECG at the Week 24/Baseline and Week 52visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal liver test results (AST or ALT > 3 x ULN) that develop during the Open-Label Treatment Period will be reported within 24 hours of study personnel awareness.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.
Risk of Estradiol (1.0 mg)/Norethindrone Acetate (0.5 mg) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 24/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; QTc = corrected QT interval; QTcF = QT interval by the Fridericia correction; PLD = phospholipidosis; ULN = upper limit of normal.

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 Investigator Site File 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 (SAP) will describe the detailed statistical methods and analyses for this study.

All efficacy and safety measures over the course of both the parent and extension studies will be presented by the parent study treatment group using descriptive statistics. No formal treatment comparisons will be performed for this extension study. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.

9.1. Randomization Methods

This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for 80 weeks.

9.2. Analysis Populations

Efficacy data analyses will be performed on the modified Intent-to-Treat (mITT) Population, defined as all patients who were randomized in a parent study (MVT-601-3101 or MVT-601-3102) and who have received any amount of randomized study drug.

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

The analysis methods for safety and efficacy endpoints are the same as those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Justification

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

9.4. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the mITT Population.

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

The point estimates and 2-sided 95% confidence intervals (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic

medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline in the parent study greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline. Patients who had a pain reduction less than the pre-determined threshold or who had an increase in the use of analgesics for endometriosis-associated pain will be considered non-responders. The pain reduction thresholds will be determined for NMPP and dysmenorrhea separately (see the SAP for details) for the parent studies and these same thresholds will be applied to this study.

Baseline values are calculated using the Baseline pain assessment period, which is defined as the period from the date of the first dose of placebo in the parent study Run-In Period through the day prior to the first dose of randomized study drug. Patients' average NRS pain scores and use of rescue analgesic medications for endometriosis-associated pain (dysmenorrhea or NMPP) will be compared between a given visit-specific pain assessment period (eg, Week 28, Week 32, etc.) and the Baseline pain assessment period. The visit-specific pain assessment period is defined as the last 35 calendar days immediately prior to and including the last dose of study drug treatment received prior to the visit date.

For any pain assessment period (Baseline or visit-specific), the average NRS scores will be calculated for dysmenorrhea and NMPP separately. An average NRS score for dysmenorrhea is calculated as the average NRS score over the days with menses during a given pain assessment period. An average NRS score for NMPP is calculated as the average NRS score over the days without menses during a given pain assessment period. The analgesic use for a given pain assessment period is summarized by total dose count defined as the average daily dose count taken during the given pain assessment period multiplied by 35. Additional details on calculating dose counts and on the precise definition of an increase in analgesic use will be provided in the SAP.

Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies at Week 52 and Week 104.

- Change from the parent study Baseline in the EHP-30 Pain Domain scores;
- Change from the parent study Baseline to in the mean dysmenorrhea NRS score;
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea;
- Change from the parent study Baseline in the mean NMPP NRS score;
- Proportion of patients who are better or much better on the PGIC for NMPP;
- Change from the parent study Baseline in the mean dyspareunia NRS scores;
- Proportion of patients who are better or much better on the PGIC for dyspareunia;
- Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale;
- Change from the parent study Baseline in severity scores on the PGA for pain;

- Proportion of responders based on EHP-30 Pain Domain scores;
- Change from the parent study Baseline in function impairment on the PGA for function;
- Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
- Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B);
- Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).

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

For endpoint of proportion of responders based on EHP-30 Pain Domain scores, a responder is defined using the same within-patient score change threshold determined from the parent studies.

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.

The treatment-emergent period will be defined as the period of time from the first dose date and time of randomized study drug in the parent study 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, 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, high level term, and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

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

visit. The change from parent study Baseline to each post-baseline study visit will be presented by parent study treatment group for each laboratory test.

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

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. Electrocardiograms will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic) mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for percent change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group. The 95% CI for mean percentage change at Week 104 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104 as supportive analyses.

All data will be listed and summarized by visit. The absolute change and percent change from parent study Baseline to Weeks 36, 52, and 104 and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the parent study treatment group.

Additional analyses will be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Pharmacodynamics Analyses

The change from the parent study Baseline to Week 52 and to Week 104 in predose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.

9.7. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed at Week 52 and Week 104:

- Change from Baseline in the EHP-30 scale total score;
- Change from Baseline in the EHP Work Domain score;
- Change from parent study Baseline in the EQ-5D-5L.

9.8. Interim Analyses

An interim analysis will be conducted at Week 52 in which all efficacy and safety endpoints will be assessed as described above. A clinical study report will be generated based on these data to support submission of one-year data.

9.9. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

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

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB- or IEC-approved informed consent form for documenting

written informed consent that contains all elements required by national, state, local, and institutional regulations or requirements. Each informed consent form will be appropriately signed and dated by the patient 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, US, 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 Investigator Site File. 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 lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, accountability, and returned or destroyed study product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient 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, European Union (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. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements.

Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

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

10.2.3. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies) at Week 52 and a second clinical study report will be prepared at the end of the study (Week 104). 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). 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.

11. REFERENCES

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12. APPENDICES

Appendix 1. 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).

Appendix 2. Daily eDiary

Version 3 MY80005-eDiary
US English Screen Report 23May2017

Screen report: my80005-eDiary Subject Facing

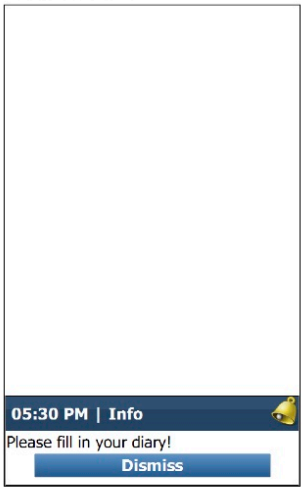
Localized texts are displayed in English.

Contents

Version 3
US English Screen Report

MY80005-eDiary
23May2017

1 Common



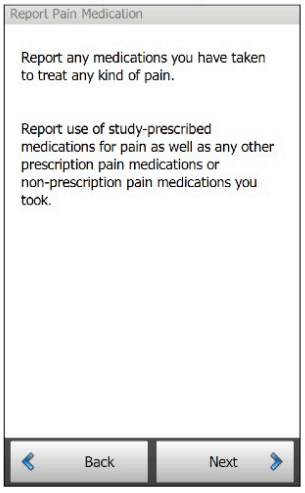
Message 1

Note: Time will populate per device

Version 3
US English Screen Report

MY80005-eDiary
23May2017

2 Form: MedReport



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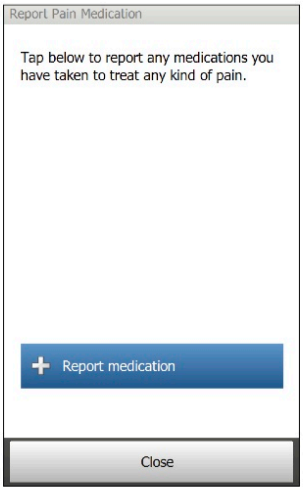

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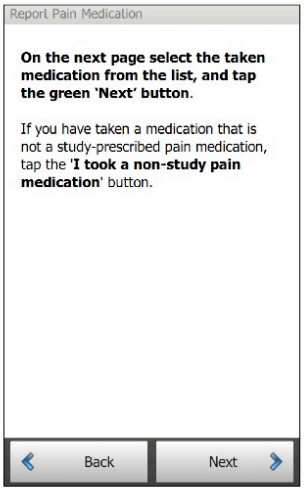

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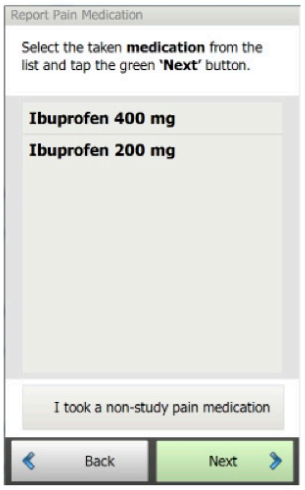

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Note: Medications will show per patient set up

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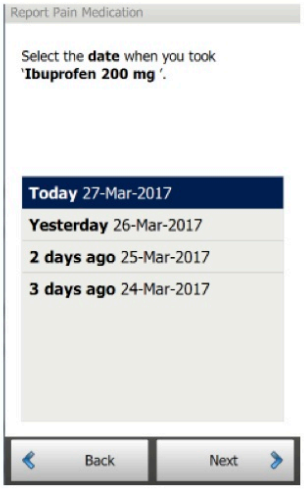


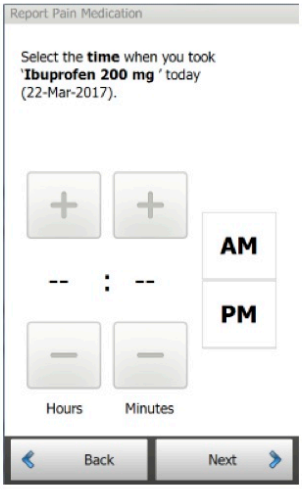
Screen 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2

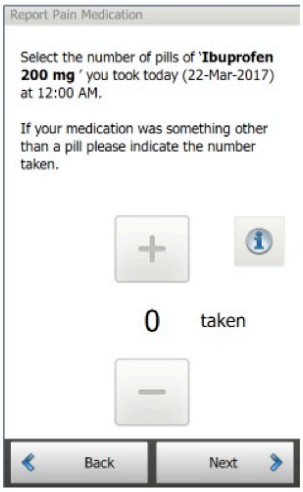


Screen 6

Message 3

Note: Medication Name and Date will show per device

Message 4



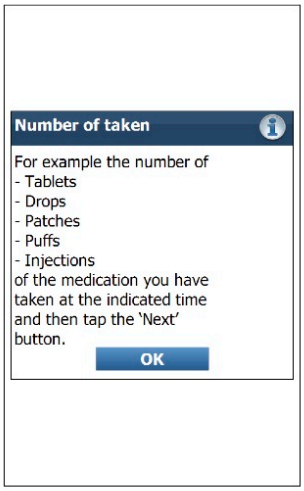
Screen 7

Message 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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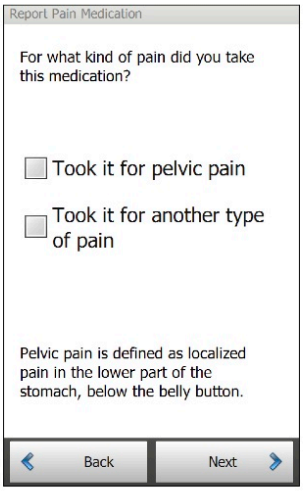

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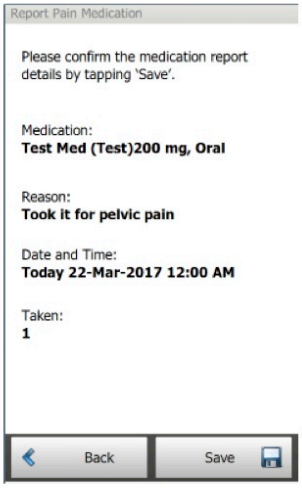
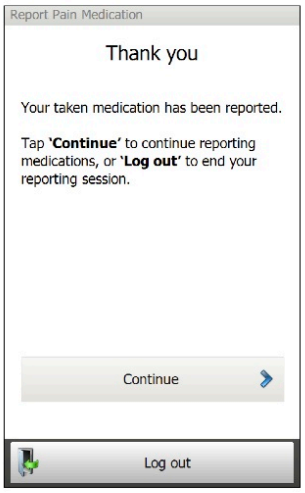


Screen 9

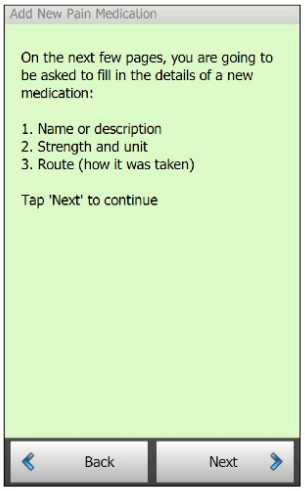
Note: 'Medication', 'Reason', 'Date and Time', 'Taken' will show per patient selection



Screen 10

Version 3
US English Screen Report

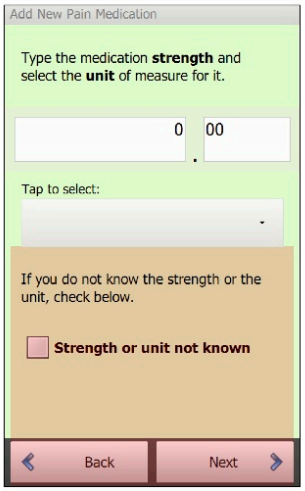
MY80005-eDiary
23May2017



Screen 11

Screen 12

Message 7



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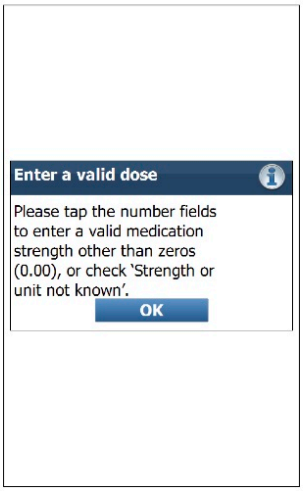
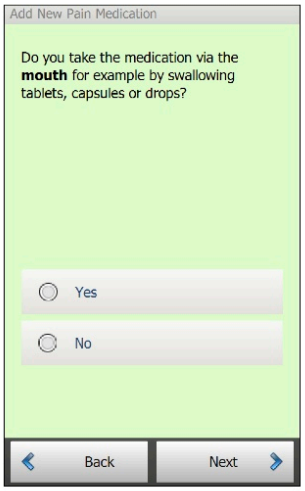


Message 8

Message 9

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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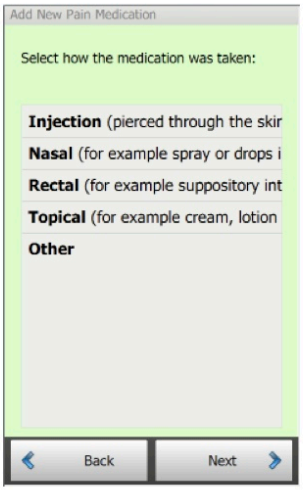

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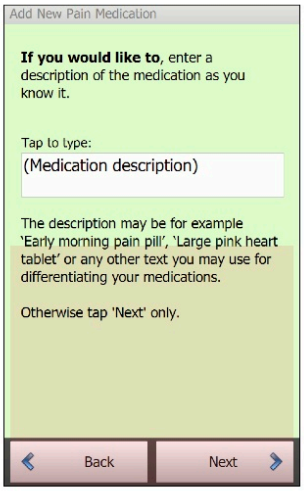

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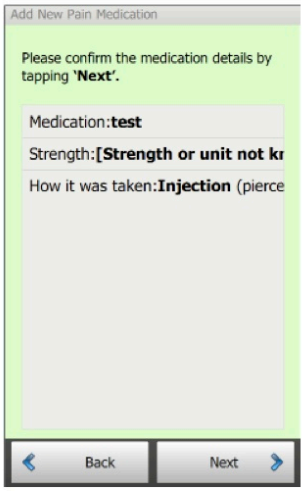
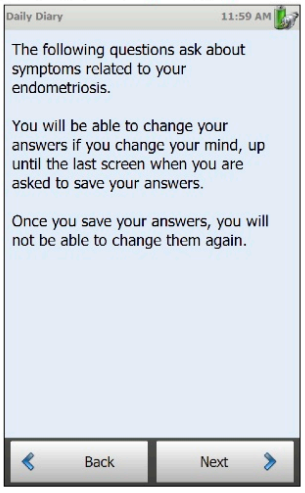


Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

3 Form: Daily Diary



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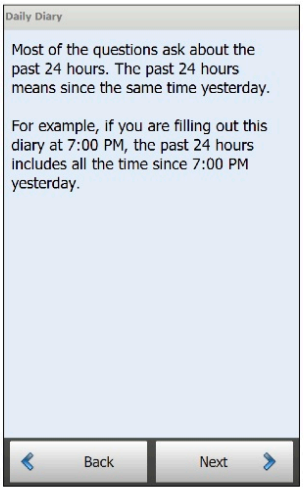

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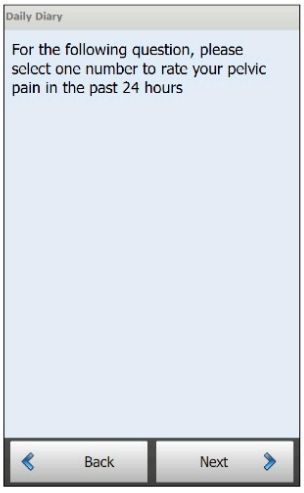

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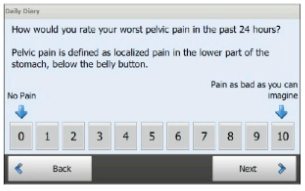

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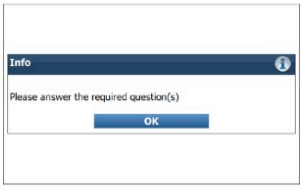

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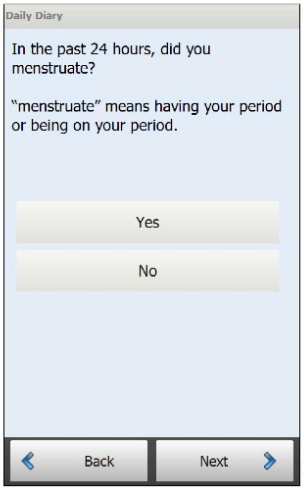
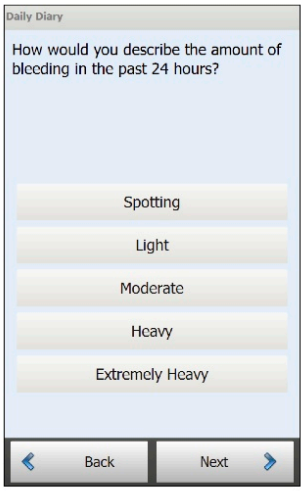


Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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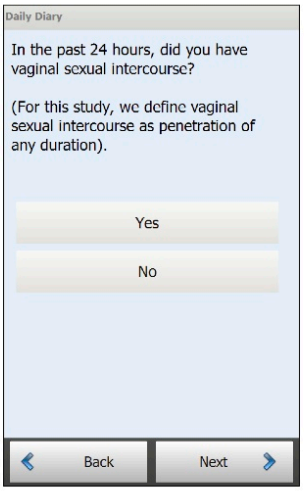

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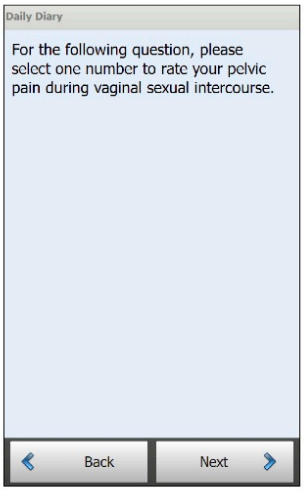

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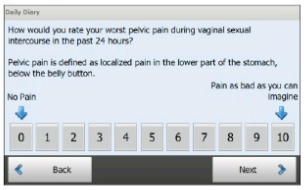

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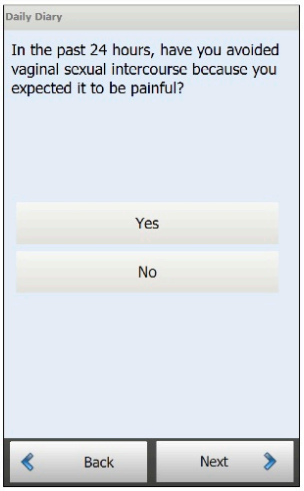

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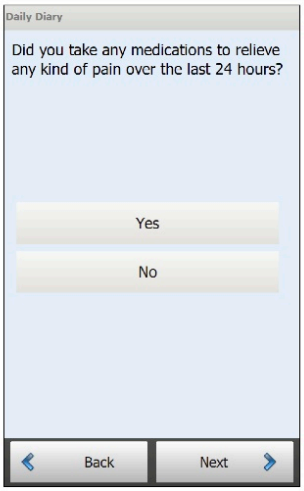
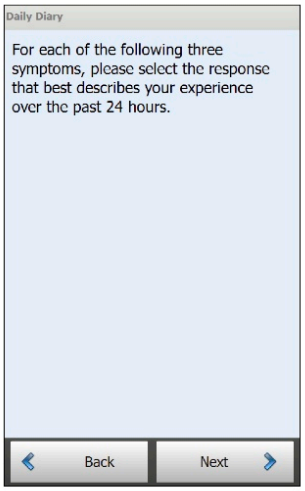


Screen 11

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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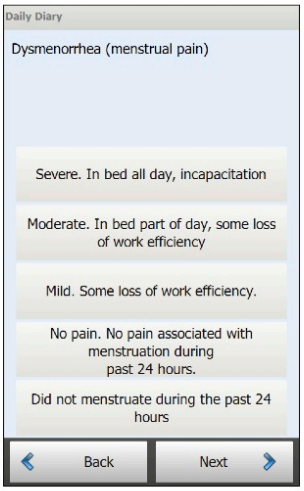

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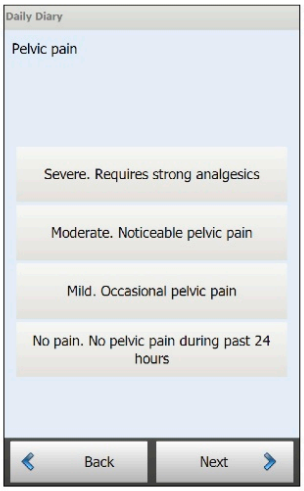

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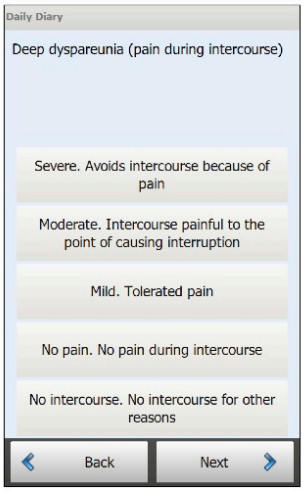

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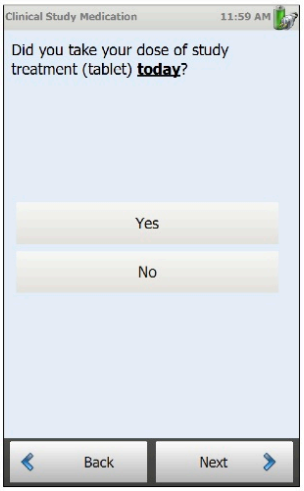

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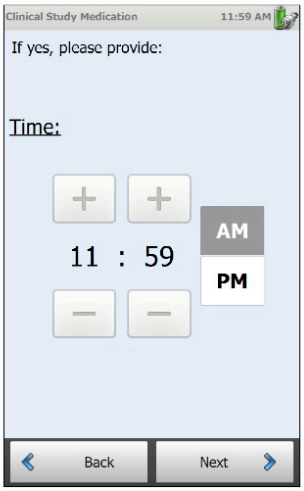
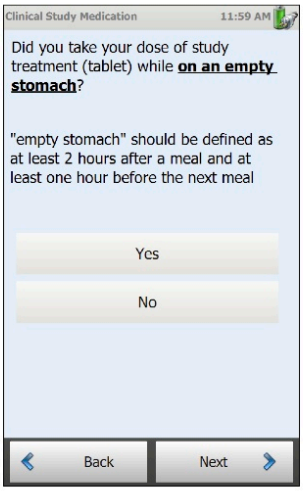


Screen 17

Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2



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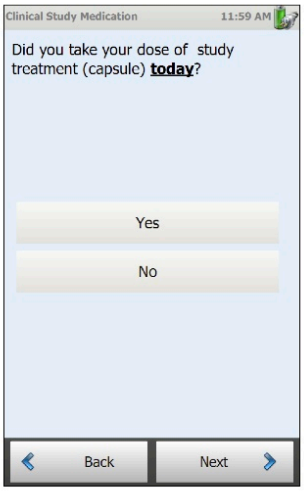
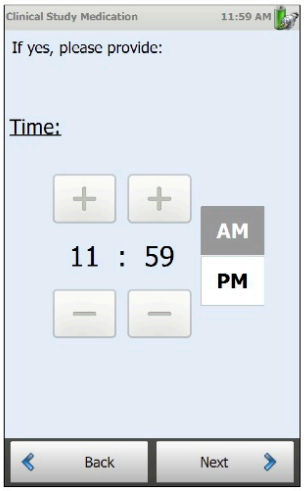
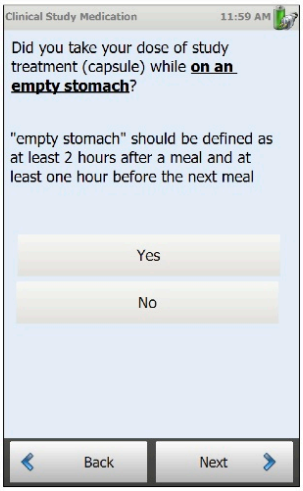


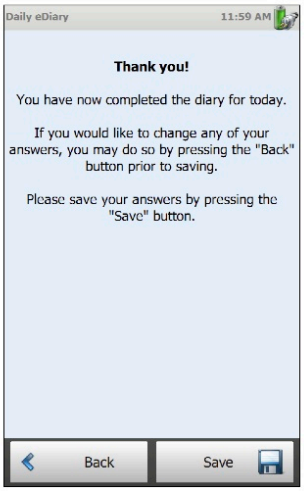
Screen 19



Screen 20



Screen 21



Screen 22

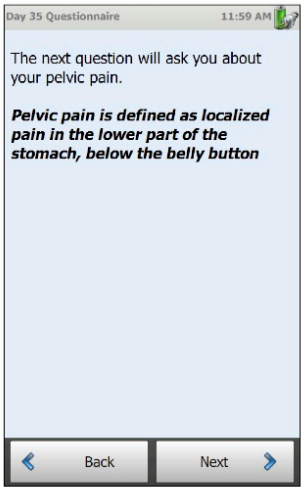
Version 3
US English Screen Report

MY80005-eDiary
23May2017

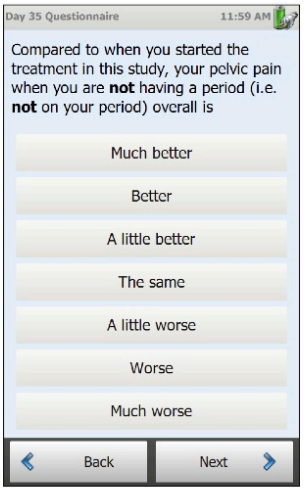
Message 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

4 Form: PGIC-NMPP

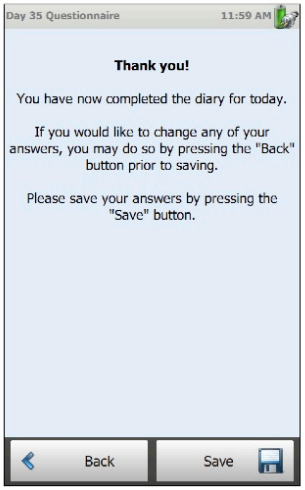


Screen 1

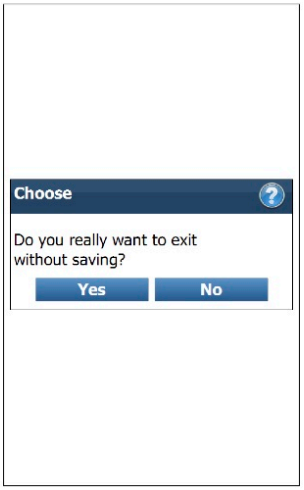


Screen 2

Message 1



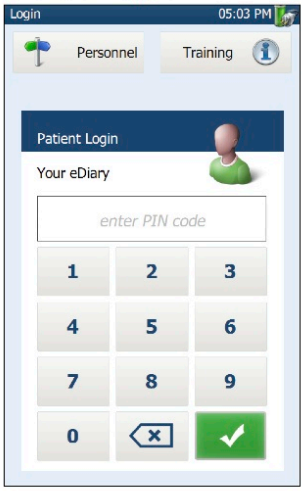
Screen 3



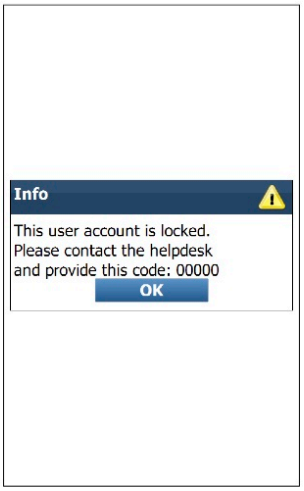
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

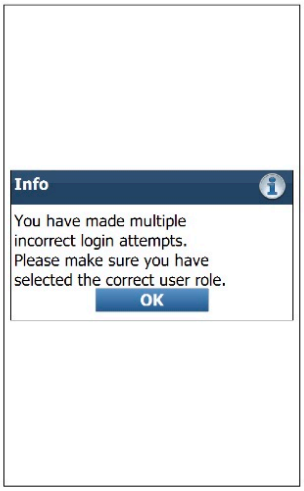
5 Form: Login



Screen 1



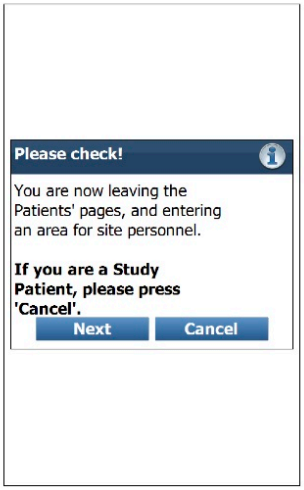
Message 1



Message 2

Message 3

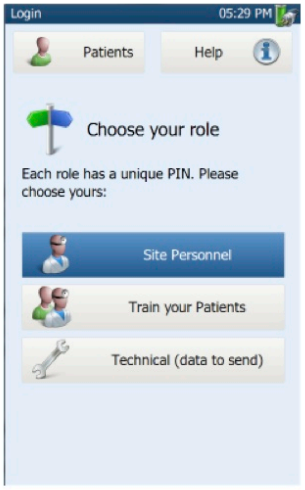
Message 4



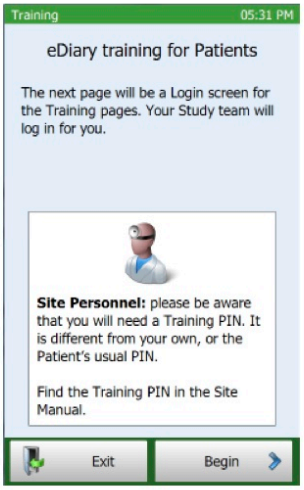
Message 5

Version 3
US English Screen Report

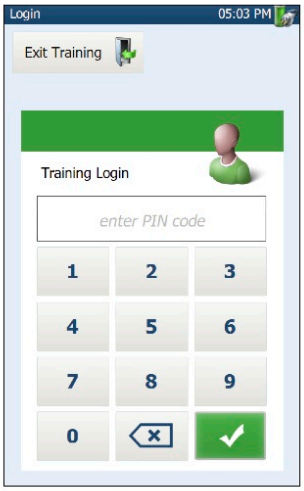
MY80005-eDiary
23May2017



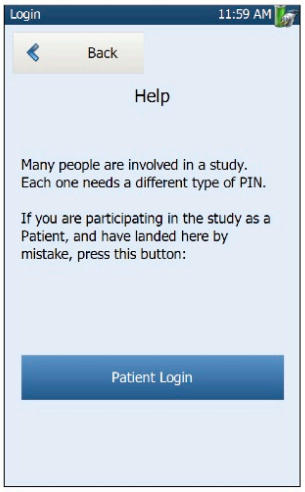
Screen 2



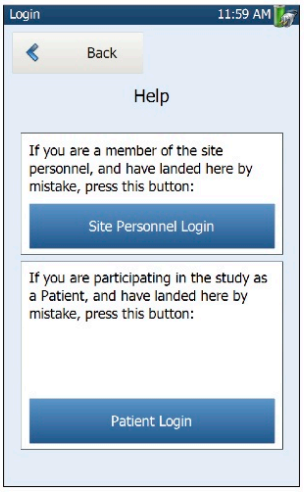
Screen 3



Screen 4



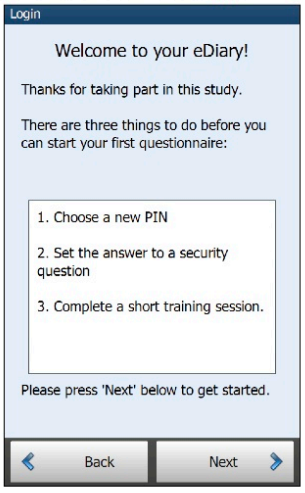
Screen 5



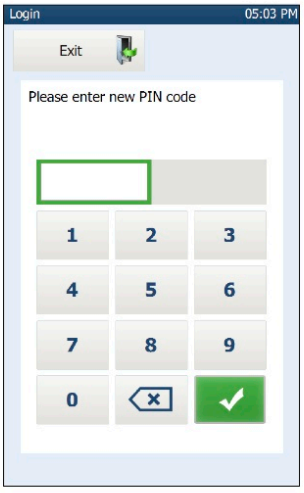
Screen 6

Version 3 MY80005-eDiary
US English Screen Report 23May2017

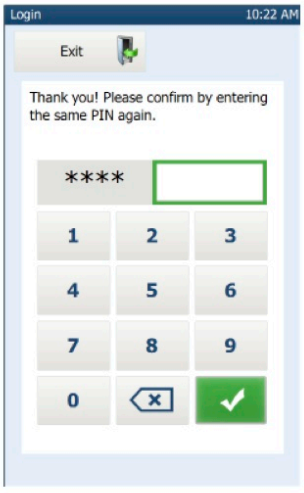
6 Form: PIN change



Screen 1



Screen 2

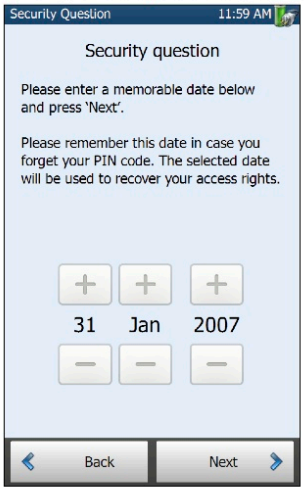


Screen 3

Message 1

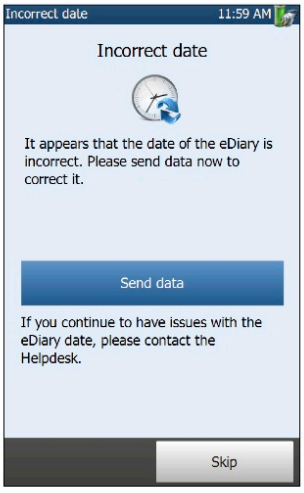
Version 3 MY80005-eDiary
US English Screen Report 23May2017

7 Form: Subject main menu

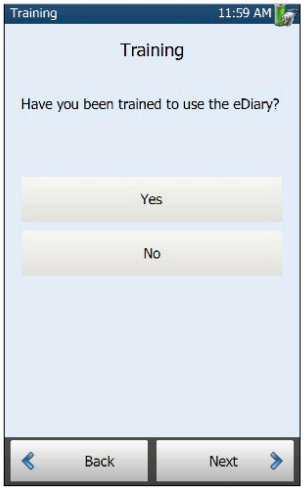


Screen 1

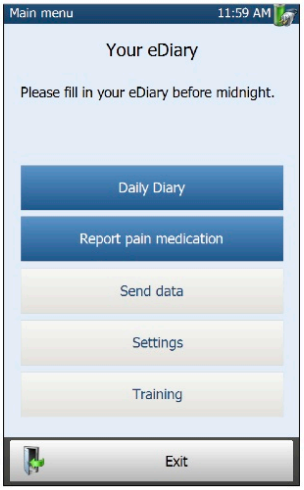
Message 1



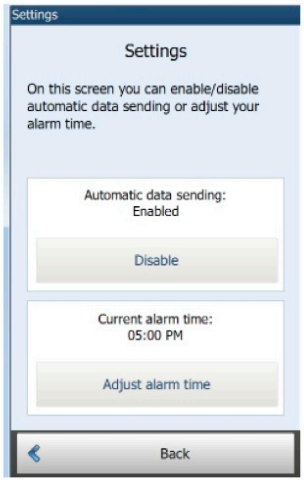
Screen 2



Screen 3



Screen 4



Screen 5

Note: Time will update per device

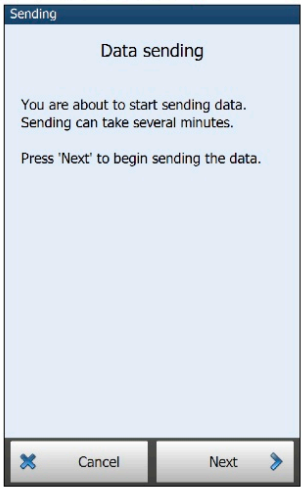
Version 3
US English Screen Report

MY80005-eDiary
23May2017

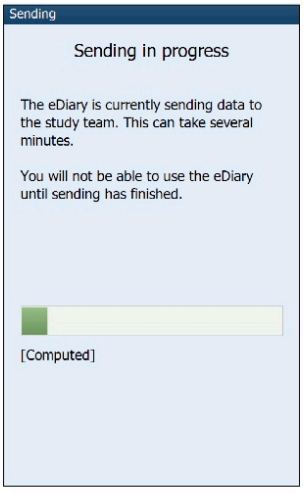
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

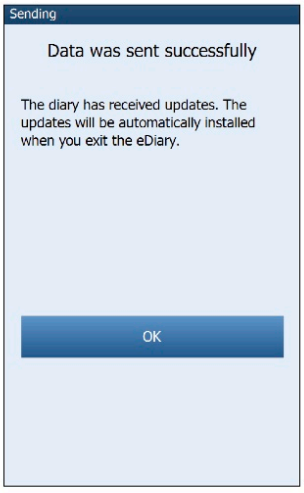
8 Form: Sending



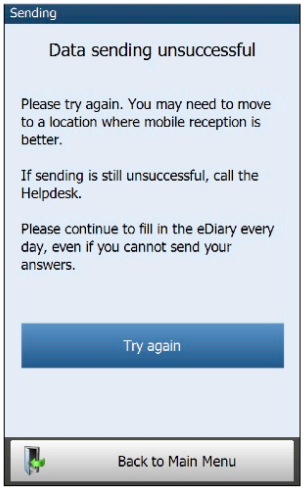
Screen 1



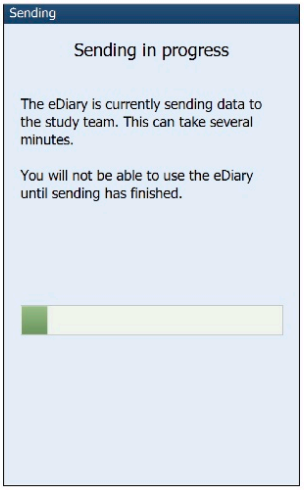
Screen 2



Screen 3



Screen 4

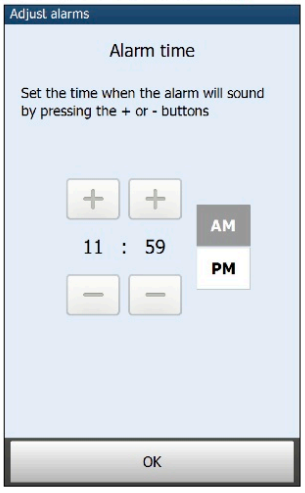


Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017

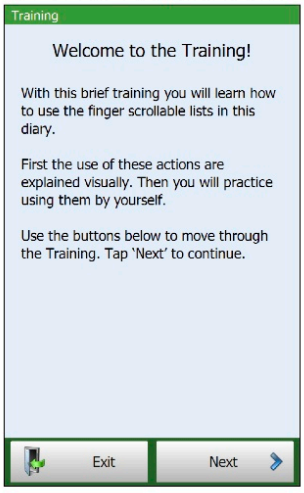
9 Form: AlarmSetup



Screen 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

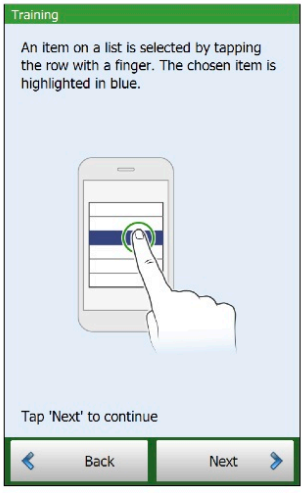
10 Form: Subject training diary



Screen 1

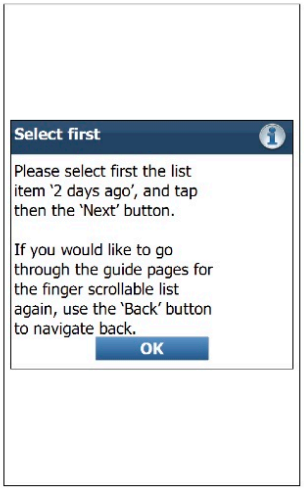
Message 1

Message 2



Screen 2

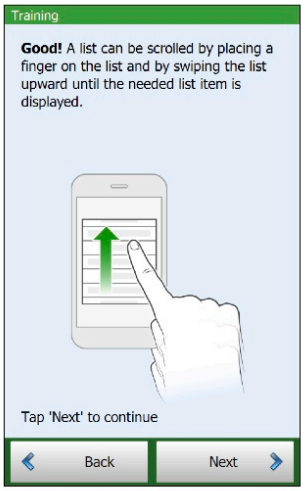
Screen 3



Message 3

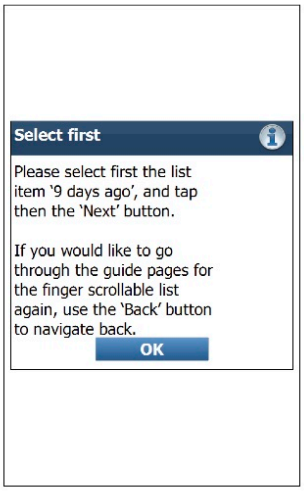
Version 3
US English Screen Report

MY80005-eDiary
23May2017

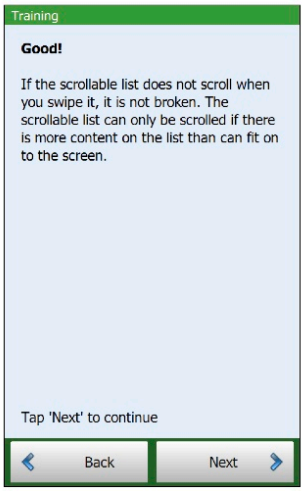


Screen 4

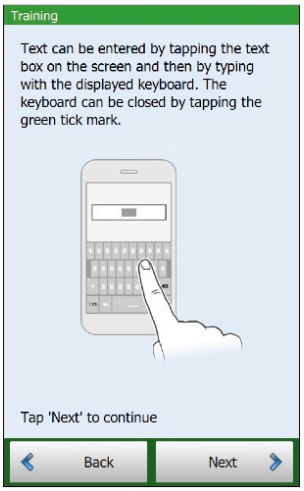
Screen 5



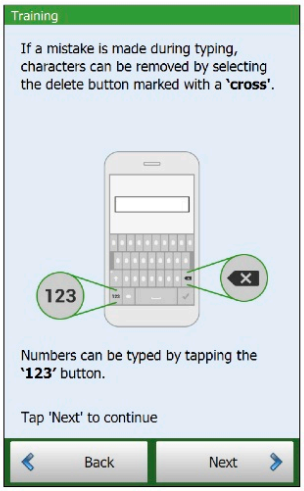
Message 4



Screen 6



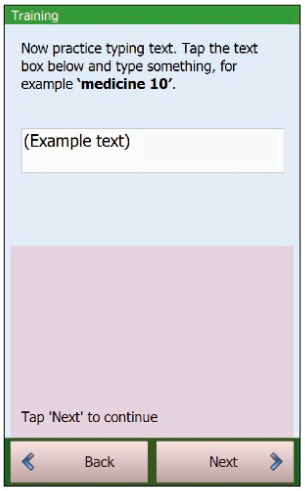
Screen 7



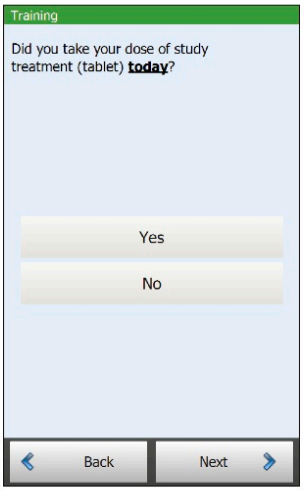
Screen 8

Version 3
US English Screen Report

MY80005-eDiary
23May2017

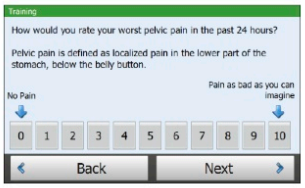


Screen 9



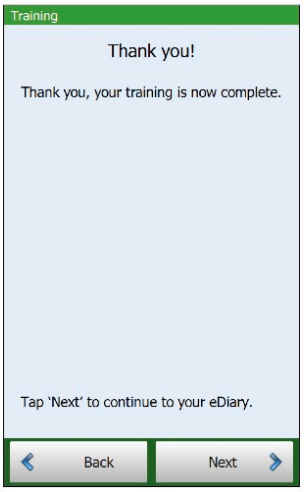
Screen 10

Message 5



Screen 11

Note: Screen will show latteraly on device



Screen 12

Version 3
US English Screen Report

MY80005-eDiary
23May2017

11 Keyboards

Appendix 3. 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.	☐	☐	☐	☐	☐
2.	☐	☐	☐	☐	☐
3.	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐
5.	☐	☐	☐	☐	☐
6.	☐	☐	☐	☐	☐

Please check one box for each question

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

	Never	Rarely	Sometimes	Often	Always
7.	☐	☐	☐	☐	☐
8.	☐	☐	☐	☐	☐
9.	☐	☐	☐	☐	☐
10.	☐	☐	☐	☐	☐
11.	☐	☐	☐	☐	☐
12.	☐	☐	☐	☐	☐
13.	☐	☐	☐	☐	☐
14.	☐	☐	☐	☐	☐

Please checked one box for each question

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

	Never	Rarely	Sometimes	Often	Always
15.	☐	☐	☐	☐	☐
16.	☐	☐	☐	☐	☐
17.	☐	☐	☐	☐	☐
18.	☐	☐	☐	☐	☐
19.	☐	☐	☐	☐	☐
20.	☐	☐	☐	☐	☐
21.	☐	☐	☐	☐	☐
22.	☐	☐	☐	☐	☐

Checked one box for each question

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

	Never	Rarely	Sometimes	Often	Always
23.	☐	☐	☐	☐	☐
24.	☐	☐	☐	☐	☐
25.	☐	☐	☐	☐	☐
26.	☐	☐	☐	☐	☐
27.	☐	☐	☐	☐	☐
28.	☐	☐	☐	☐	☐
29.	☐	☐	☐	☐	☐
30.	☐	☐	☐	☐	☐

Please checked one box for each question .

Appendix 4. 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 ❑

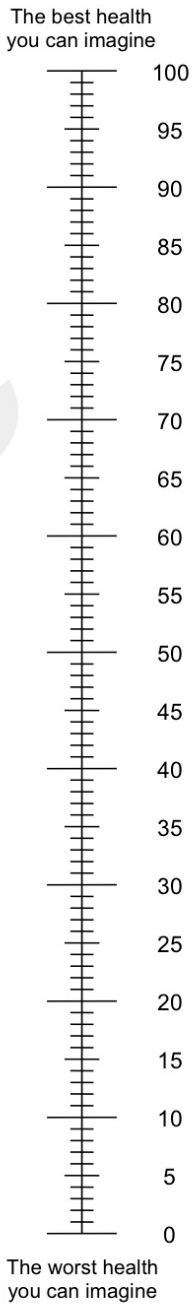
ANXIETY / DEPRESSION

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 5. 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 function)

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

Not at all
Minimally
Moderately
Significantly
Very significantly

Note: PGA for function is administered via a paper questionnaire.

Appendix 6. Endometriosis Health Profile - Work Domain

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.***

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

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

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

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

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

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

Recommended tests:

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

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

CBC = complete blood count; INR = international normalized ratio.

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

AMENDMENT 2: SUMMARY OF CHANGES

The MVT-601-3103 protocol has been amended as described in the table below. The primary purpose of the amendment is to extend the study from 52 weeks of treatment to 104 weeks of treatment, inclusive of the 24 weeks of treatment in the parent study. Additionally, the protocol is being amended to include an endometrial biopsy at Week 52 and an optional endometrial biopsy at Week 104.

A detailed list of changes is described below, where deleted text is indicated by ~~strikethrough~~ and new text is indicated with **bold** formatting. Note that the correction of typos, minor clarifications, and minor wording changes to improve readability, understanding, and consistency may not be included in this table.

Section Item	Original	Amendment 2	Rationale
Title Page Version and Effective Date	Original: 06-NOV-2017 Amendment 1: 20-MAR-2018	Original: 06 NOV 2017 Amendment 1: 20 MAR 2018 **Amendment 2: 11 Dec 2018**	Updated the effective date of the current amendment.
Header	Amendment ~~1, 20 MAR~~ 2018	Amendment **2, 11 Dec 2018**	Updated effective date of current amendment.
Sponsor Signature Page	Protocol Number: MVT-601-3103	Protocol Number: MVT-601-3103 **Amendment 2**	Updated the current version of the protocol.
Sponsor Signature Page	PPD PPD PPD		Updated signatories.
List of Abbreviations	~~EOT: end of treatment~~	**BP: blood pressure** **CBC: complete blood count** **EU: European Union** **HR: heart rate** **IVRS: interactive voice response system** **IWRS: interactive web response system** **SNRI: serotonin and norepinephrine reuptake inhibitor** **SSRI: selective serotonin reuptake inhibitor** **TCA: tricyclic antidepressant** **W: week**	Updated list of abbreviations to reflect abbreviations included in the protocol.
Synopsis Study Objectives	Primary Efficacy ~~Objective~~ To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	Primary Efficacy **Objectives** **To be assessed at Week 52** • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	Updated primary objective to reflect extending the study to 104 total weeks of treatment to evaluate the long-term efficacy and safety of relugolix 40 mg once daily co-administered with low-dose E2/NETA. Additionally, changes reflect the plan to conduct two analyses, the first using data collected through 52 weeks of treatment, and the second using

Section Item	Original	Amendment 2	Rationale
		To be assessed at Week 104 • **To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.**	data collected through 104 weeks of treatment.
Synopsis Study Objectives	Secondary Efficacy Objectives To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate ~~for up to 52 weeks~~, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: Safety Objectives To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to ~~52~~ weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: Pharmacodynamic Objective To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to ~~52~~ weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	Secondary Efficacy Objectives **To be assessed at Week 52 and Week 104** To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: • **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 EHP-30 Pain Domain;** Safety Objectives To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to **104** weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: Pharmacodynamic Objective	Updated secondary objectives to reflect extending the study to 104 total weeks of treatment and the intention to conduct analyses on data through Week 52 and Week 104. Additionally, secondary efficacy endpoint was added in the synopsis to match the endpoints listed in the body of the protocol.

Section Item	Original	Amendment 2	Rationale
	Exploratory Objective To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to ~~52~~ weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to **104** weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol. Exploratory Objective To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to **104** weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	
Synopsis Study Design	All patients will receive oral relugolix 40 mg once daily coadministered with -lowdose- estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to ~~28~~ weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to ~~52~~ weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate.	All patients will receive **open-label** oral relugolix 40 mg once daily co-administered with low-dose- estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to **80** weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to **104** weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate.	Added clarification on the open-label nature of the study and updated timing elements to reflect extension to 104 total weeks of treatment.
Synopsis Study Design	Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be	Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be	Added clarification that the first dose of study drug could be initiated up to 10 days after completion of the parent study to allow for logistical issues.

Section Item	Original	Amendment 2	Rationale
	eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg coadministered- with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for ~~28~~ weeks.	eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for **80** weeks. **If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).**	
Synopsis Study Design	During the ~~28~~-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the electronic diary (eDiary).	During the **80**-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the electronic diary (eDiary).	Updated duration of treatment to reflect extension of treatment.
Synopsis Study Design	At the Week 36~~ visit~~ and Week ~~52~~/Early Termination ~~visit~~, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).	At the Week 36**, Week 52,** and Week **104**/Early Termination **visits**, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).	Updated timing of DXA scans to reflect extension of treatment.
Synopsis Study Design	~~Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit (or most recent~~	**Determination of bone mineral density by DXA at Early Termination and follow-up of**	Added clarification for when DXA scans would be

Section Item	Original	Amendment 2	Rationale
	~~scan, if the Week 52/ET scan was not done) relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (±1) months after the last dose of study medication.~~	**findings will proceed according to the following rules:** • **For Early Termination occurring between Week 24 and Week 52:** – **For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event.** **Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.** – **For Early Termination occurring after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.** **Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline.** **Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or**	conducted and the follow-up rules for DXA results.

Section Item	Original	Amendment 2	Rationale
		total hip was > 3%, relative to the parent study baseline. • **For Early Termination occurring between Week 52 and Week 104:** – **DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.** – **Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.**	
Synopsis Study Design	If the patient enrolls directly into another relugolix clinical study upon completion of the Week ~~52~~ visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (±1) months and status of menstruation recovery, may be waived.	If the patient enrolls directly into another relugolix clinical study upon completion of the Week **104** visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (±1) months and status of menstruation recovery, may be waived.	Updated study timing to reflect extension of treatment.
Synopsis Exclusion Criteria	The presenting visual acuity score has decreased by ~~10~~ or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;	**11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):** **a. 90 or lower and five or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or** b. The presenting visual acuity score has decreased by **ten** or more points at the	Clarified visual acuity criteria.

Section Item	Original	Amendment 2	Rationale
		Week 24/Baseline visit relative to the parent study Baseline visit.	
Synopsis Duration of Treatment	Study treatment will be self-administered for ~~28~~ weeks (Open-Label Treatment Period).	Study treatment will be self-administered for **80** weeks (Open-Label Treatment Period).	Updated study timing to reflect extension of treatment.
Synopsis Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week ~~52~~) for the following parent study treatment groups:	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and **Week 52, and between** the **parent study Baseline and the** end of the extension study (Week **104**) for the following parent study treatment groups:	Updated to reflect extension of treatment.
Synopsis Criteria for Evaluation	Primary Efficacy Endpoints • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores.	Primary Efficacy Endpoints **Week 52** • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. **Week 104** • **Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores;** • **Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores.**	Updated endpoints to reflect extension of treatment.
Synopsis Criteria for Evaluation	Secondary Efficacy Endpoints • Change from the parent study Baseline ~~to Week 52~~ in the EHP-30 Pain Domain scores;	Secondary Efficacy Endpoints	Updated endpoints to reflect extension of treatment.

Section Item	Original	Amendment 2	Rationale
	• Change from the parent study Baseline ~~to Week 52/end of treatment (EOT)~~ in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea ~~at Week 52/EOT~~; • Change from the parent study Baseline ~~to Week 52/EOT~~ in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP ~~at Week 52/EOT~~; • Change from the parent study Baseline ~~to Week 52/EOT~~ in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia ~~at Week 52/EOT~~; • Change from the parent study Baseline ~~to Week 52/EOT~~ in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline ~~to /EOT~~ in severity scores on the PGA for pain; • Proportion of responders ~~at Week 52/EOT~~ based on their EHP-30 Pain Domain score; • Change from the parent study Baseline ~~to Week 52/EOT~~ in function impairment on the PGA for function; • Change from the parent study Baseline ~~to Week 52/EOT~~ in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);	**To be assessed at Week 52 and Week 104, unless otherwise specified** • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea **(at Week 52 only)**; • Change from the parent study Baseline in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP **(at Week 52 only)**; • Change from the parent study Baseline in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia **(at Week 52 only);** • Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline in severity scores on the PGA for pain; • Proportion of responders based on their EHP-30 Pain Domain score; • Change from the parent study Baseline in function impairment on the PGA for function; • Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);	

Section Item	Original	Amendment 2	Rationale
	• Change from the parent study Baseline pain assessment period ~~to Week 52/EOT~~ in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period ~~to Week 52/EOT~~ in NMPP-related functional effects (sB&B).	• Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).	
Synopsis Criteria for Evaluation	Safety Endpoints • Incidence of adverse events; • Percent change from the parent study Baseline ~~to Week 52~~ in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.	Safety Endpoints **To be assessed at Week 52 and Week 104** • Incidence of adverse events; • Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.	Updated endpoints to reflect extension of treatment.
Synopsis Criteria for Evaluation	Pharmacodynamic Endpoint • Change from parent study Baseline ~~to Week 52~~ in pre-dose concentrations of serum estradiol. Exploratory Endpoints • Change from Baseline ~~to Week 52/EOT~~ in the EHP-30 scale total score; • Change from Baseline ~~to Week 52/EOT~~ in the EHP Work Domain score; • Change from parent study Baseline ~~to Week 52/EOT~~ in the EQ-5D-5L.	Pharmacodynamic Endpoint **To be assessed at Week 52 and Week 104** • Change from parent study Baseline in predose concentrations of serum estradiol. Exploratory Endpoints **To be assessed at Week 52 and Week 104** • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.	Updated endpoints to reflect extension of treatment.
Synopsis Statistical Methods		**There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.**	Clarified plan to conduct two analyses (one with data through 52 weeks of treatment and one with data through 104 weeks of treatment) and develop a

Section Item	Original	Amendment 2	Rationale
			separate clinical study report for each analysis.
Synopsis Statistical Methods	Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52).	Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52 **or Week 104**).	Updated to reflect extension of treatment.
Synopsis Statistical Methods	Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, and Week ~~52~~/Early Termination visits. The absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.	Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, **Week 52,** and Week **104**/Early Termination visits. The absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.	Updated to reflect extension of treatment.
Synopsis Statistical Methods	The mean percentage change ~~at Week 52~~ from parent study Baseline in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant.	The mean percentage change from parent study Baseline **to Week 52** in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > 2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant. **The 95% CI for mean**	Updated to reflect extension of treatment, and to provide a description of analyses to be conducted on data from Week 104.

Section Item	Original	Amendment 2	Rationale
		percentage change at Week 104 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104 as supportive analyses.	
Table 1-1 Schedule of Activities for Study MVT-601-3103		*Note: Week 65, Week 78, Week 91, and Week 104, along with corresponding assessments/activities were added to the Schedule of Activities. Telephone contact at Week 57, Week 71, Week 85, and Week 98 was added (an 'X' was added to the nearest scheduled visit in the Schedule of Activities).*	Updated to reflect extension of treatment, add telephone contact at Weeks 57, 71, 85, and 98.
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote a	a The Week 52 visit should occur on or after the 1-year anniversary of ~~Study~~ Day 1 of the parent study.	a The Week 52 visit should occur on or after the 1-year anniversary of **Baseline** Day 1 of the parent study**, and the Week 104 visit should occur on or after the 2-year anniversary of Baseline Day 1 of the parent study.**	Updated to reflect extension of treatment.
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote i	*Footnote i and subsequent footnotes were shifted by one to accommodate a new footnote.*	**i The Week 52 and Week 104 physical examinations will include a breast examination.**	Clarified which physical examinations would include a breast examination.
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote l	~~l~~ Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, and Week ~~52~~. At the Week 24/Baseline visit ~~and~~ Week 52 visit, additional tests include: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.	**m** Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, **Week 52, Week 65, Week 78, Week 91,** and Week **104**. At the Week 24/Baseline visit, Week 52 visit, **and Week 104 visit,** additional tests **will** include **the following**: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.	Updated to reflect extension of treatment.
Table 1-1 Schedule of Activities for Study	~~n~~ For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week ~~52~~/Early Termination, collect ~~samples~~ for analysis of estradiol	**o** For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week **104**/Early Termination, collect **a sample** for analysis of estradiol concentrations	Updated to reflect extension of treatment.

Section Item	Original	Amendment 2	Rationale
MVT-601-3103 Footnote n	concentrations only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are co~~mp~~leted.	only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are col**lec**ted.	
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote o	~~o At the Week 24/Baseline visit, transition the~~ patient ~~within her~~ eDiary ~~from~~ the parent study ~~to MVT-601-3103. The eDiary data collection will include~~ NRS pain scores, menstruation information ~~(including severity of bleeding),~~ analgesic drug use, date and time of study drug administration, and sB&B scale scores.	**p All women enrolled in the study will continue to use the** patient eDiary **dispensed in the** parent study**. 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 **until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.**	Added clarification on the timing of eDiary entries.
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote r	~~r Patients with a bone mineral density loss of > 3% at their Week 52/Early Termination visit (or most recent scan if the Week 52/Early Termination visit was not done) relative to parent study Baseline measurement will undergo a follow-up bone densitometry scan at 6 (±1) months and will be contacted to question them about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.~~	**s Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed based on the timing of the Early Termination visit. For Early Termination occurring after Week 24 and before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event, and follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. For Early Termination occurring after Week 36 and before Week 52, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is**	Added clarification for when DXA scans would be conducted and the follow-up rules for DXA results.

Section Item	Original	Amendment 2	Rationale
		required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2% or most recent DXA result was after Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. For Early Termination occurring between Week 52 and Week 104, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.	
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote s	~~s~~ Endometrial biopsies are to be done per instructions in the parent study. ~~See the Laboratory Manual for guidance on~~ handling and shipping ~~the~~ biopsy sample to the central laboratory for analysis. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details).	**t** Endometrial biopsies are to be done per instructions in the parent study. **Procedures for** handling and shipping biopsy sample**s** to the central laboratory for analysis **are described in the Investigator Site File**. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details**), at Week 52 for all patients. All patients are eligible for a biopsy at Week 104; however, patients will have the option to opt out.**	Updated to reflect extended duration of study and to update the referenced document. Additionally, added clarification for the addition of endometrial biopsies at Week 52 and Week 104.
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote t	~~t~~ Please see Appendix 1 for list of protocol-specified analgesics and see the ~~Study Reference Manual~~ for information on where and how to obtain protocol-specified analgesic medications by country. At the Week ~~52~~ visit, patients who will not be proceeding to another extension study will be re-dispensed or	**u** Please see Appendix 1 for list of protocol-specified analgesics and see the **Investigator Site File** for information on where and how to obtain protocol-specified analgesic medications by country. At the Week **104** visit, patients who will not be proceeding to another extension study will be re-dispensed	Updated to reflect extended duration of study and to update the referenced document.

Section Item	Original	Amendment 2	Rationale
	prescribed protocol-specified analgesic drugs, if needed, to ensure sufficient supply until the Follow-Up visit. For patients proceeding to another extension study, refer to the protocol for that next study.	or prescribed protocol-specified analgesic drugs, if needed, to ensure sufficient supply until the Follow-Up visit. For patients proceeding to another extension study, refer to the protocol for that next study.	
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote u	~~u~~ Pregnancy test must be negative before the study drug dose is administered.	**v** Pregnancy test must be negative before the study drug dose is administered. **For patients whose Baseline Day 1 visit is conducted on a different day than the parent study Week 24 visit, perform an unscheduled pregnancy test at Baseline Day 1 prior to administering the first dose of study drug.**	Updated to clarify pregnancy test procedures for patients whose parent study Week 24 visit was different than the baseline visit for this study.
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote v	~~v~~ Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week ~~52~~/Early Termination visit.	**w** Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). **If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.).** The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week **104**/Early Termination visit.	Added clarification that the first dose of study drug could be initiated up to 10 days after completion of the parent study to allow for logistical issues. Additionally, updated timing to reflect extension of study to 104 weeks of treatment.

Section Item	Original	Amendment 2	Rationale
Table 1-1 Schedule of Activities for Study MVT-601-3103 Footnote cc		**cc A telephone call will be performed at Weeks 57, 71, 85, and 98. The following activities should be completed: a concomitant medication review, evaluation of adverse events, a reminder of compliance with non-hormonal contraception requirements and the need to call the investigator if pregnancy is suspected, and a review of eDiary and study medication compliance.**	Added to clarify when telephone contact would be made and what would be reviewed during the telephone contact.
Section 3 Study Objectives and Endpoints	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and the end of the extension study (Week ~~52~~) for the following parent study treatment groups:	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and **Week 52, and between** the **parent study Baseline** the end of the extension study (Week **104**) for the following parent study treatment groups:	Updated to reflect extending the study to 104 total weeks of treatment to evaluate the long-term efficacy and safety of relugolix 40 mg once daily co-administered with low-dose E2/NETA. Additionally, changes reflect the plan to conduct two analyses, the first using data collected through 52 weeks of treatment, and the second using data collected through 104 weeks of treatment.
Section 3 Study Objectives and Endpoints	To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	**To be assessed at Week 52** • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. **To be assessed at Week 104**	Updated secondary objectives to reflect extending the study to 104 total weeks of treatment and the intention to conduct analyses on data through Week 52 and Week 104.

Section Item	Original	Amendment 2	Rationale
		• **To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.**	
Section 3 Study Objectives and Endpoints	• Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores.	**To be assessed at Week 52** • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. **To be assessed at Week 104** • **Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores;** • **Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores.**	Updated objectives to reflect extending the study to 104 total weeks of treatment and the intention to conduct analyses on data through Week 52 and Week 104.
Section 3 Study Objectives and Endpoints	To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate ~~for up to 52 weeks~~, among patients who previously completed a 24-week treatment period in one of	**To be assessed at Week 52 and Week 104** To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week	Updated objectives to reflect extending the study to 104 total weeks of treatment and the intention to conduct analyses

Section Item	Original	Amendment 2	Rationale
	the parent studies (MVT-601-3101 or MVT-601-3102), on the following:	treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following:	on data through Week 52 and Week 104.
Section 3 Study Objectives and Endpoints	Secondary Efficacy Endpoints • Change from the parent study Baseline ~~to Week 52~~ in the EHP-30 Pain Domain scores; • Change from the parent study Baseline ~~to Week 52/end of treatment (EOT)~~ in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea ~~at Week 52/EOT~~; • Change from the parent study Baseline ~~to Week 52/EOT~~ in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP ~~at Week 52/EOT~~; • Change from the parent study Baseline ~~to Week 52/EOT~~ in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia ~~at Week 52/EOT~~; • Change from the parent study Baseline ~~to Week 52/EOT~~ in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline ~~to Week 52/EOT~~ in severity scores on the PGA for pain; • Proportion of responders ~~at Week 52/EOT~~ based on their EHP-30 Pain Domain score;	Secondary Efficacy Endpoints **To be assessed at Week 52 and Week 104, unless otherwise specified** • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea **(at Week 52 only)**; • Change from the parent study Baseline in the mean NMPP NRS score; • Proportion of patients who are better or much better on the PGIC for NMPP **(at Week 52 only)**; • Change from the parent study Baseline in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia **(at Week 52 only);** • Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline in severity scores on the PGA for pain; • Proportion of responders based on their EHP-30 Pain Domain score; • Change from the parent study Baseline in function impairment on the PGA for function;	Updated endpoints to reflect extension of treatment.

Section Item	Original	Amendment 2	Rationale
	• Change from the parent study Baseline ~~to Week 52/EOT~~ in function impairment on the PGA for function; • Change from the parent study Baseline ~~to Week 52/EOT~~ in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period ~~to Week 52/EOT~~ in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period ~~to Week 52/EOT~~ in NMPP-related functional effects (sB&B).	• Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).	
Section 3 Study Objectives and Endpoints	To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to ~~52~~ weeks, among patients who previously completed a 24 week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to **104** weeks, among patients who previously completed a 24 week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	Updated objectives to reflect extension of treatment.
Section 3 Study Objectives and Endpoints	• Incidence of adverse events; • Percent change from the parent study Baseline ~~to Week 52~~ in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.	**To be assessed at Week 52 and Week 104** • Incidence of adverse events; • Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA.	Updated endpoints to reflect extension of treatment.
Section 3 Study Objectives and Endpoints	• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to ~~52~~ weeks, among patients who previously completed a 24 week	To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to **104** weeks, among patients who previously completed a 24-week treatment period in one of	Updated objectives to reflect extension of treatment.

Section Item	Original	Amendment 2	Rationale
	treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	
Section 3 Study Objectives and Endpoints	• Change from parent study Baseline ~~to Week 52~~ in pre-dose concentrations of serum estradiol.	**To be assessed at Week 52 and Week 104** • Change from parent study Baseline in predose concentrations of serum estradiol.	Updated endpoints to reflect extension of treatment.
Section 3 Study Objectives and Endpoints	• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to ~~52~~ weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to **104** weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	Updated objectives to reflect extension of treatment.
Section 3 Study Objectives and Endpoints	<u>Exploratory Endpoints</u> • Change from Baseline ~~to Week 52/EOT~~ in the EHP-30 scale total score; • Change from Baseline ~~to Week 52/EOT~~ in the EHP Work Domain score; • Change from parent study Baseline ~~to Week 52/EOT~~ in the EQ-5D-5L.	<u>Exploratory Endpoints</u> **To be assessed at Week 52 and Week 104** • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.	Updated endpoints to reflect extension of treatment.
Section 4.1 Overall Study Design	All patients will receive oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to ~~2~~8 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through	All patients will receive **open-label** oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 8**0** weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy	Added clarification on the open-label nature of the study and updated timing elements to reflect extension to 104 total weeks of treatment.

Section Item	Original	Amendment 2	Rationale
	up to ~~52~~ weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate.	and safety through up to **104** weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate.	
Section 4.1 Overall Study Design	Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg coadministered- with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for ~~28~~ weeks.	Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for **80** weeks. **If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).**	Added clarification that the first dose of study drug could be initiated up to 10 days after completion of the parent study to allow for logistical issues.
Section 4.1 Overall Study Design	During the ~~28~~-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional	During the **80**-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional	Updated timing elements to reflect extension to 80 weeks of treatment in this study.

Section Item	Original	Amendment 2	Rationale
	effects of endometriosis-associated pain (sB&B) in the ~~electronic diary (~~eDiary~~)~~.	effects of endometriosis-associated pain (sB&B) in the eDiary.	
Section 4.1 Overall Study Design	~~At the Week 36 visit and Week 52/Early Termination visit, each patient will have an assessment of bone mineral density via DXA.~~ Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density with DXA. ~~Patients with a bone mineral density loss of > 3% at the lumbar spine (L1-L4) or total hip at their Week 52/Early Termination visit (or most recent scan, if the Week 52/ET scan was not done) relative to the parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months after the last dose of study medication.~~	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density with DXA. **At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via DXA. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.**	Clarified when DXA scans were to be conducted and follow-up rules for changes in bone mineral density.
Section 4.1 Overall Study Design	If the patient enrolls directly into another relugolix clinical study upon completion of the Week ~~52~~ visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, may be waived.	If the patient enrolls directly into another relugolix clinical study upon completion of the Week **104** visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, may be waived.	Updated to reflect extension of treatment to 104 weeks.
Section 4.1 Overall Study Design	*Figure 4-1 was replaced to account for changes in study duration.*	*Figure 4-1 was replaced to account for changes in study duration.*	Updated to reflect extension of treatment to 104 weeks.
Section 4.2 Discussion of Study Design, Including Dosing	This ~~28~~-week extension study provides additional efficacy and safety data up to ~~52~~ weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study	This **80**-week extension study provides additional efficacy and safety data up to **104** weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study	Updated timing elements to reflect extension of treatment to 80 weeks for this study (104 weeks total).

Section Item	Original	Amendment 2	Rationale
	are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to ~~52~~ weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to ~~52~~ weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.	are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to **104** weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to **104** weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.	
Section 4.2 Discussion of Study Design, Including Dosing	Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily ~~(N = 101)~~ suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg.	Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg.	Omitted for readability.
Section 4.2 Discussion of Study Design, Including Dosing	Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over ~~52~~ weeks of treatment. The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through ~~52~~ weeks of treatment, as well as on vasomotor symptoms	Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over **104** weeks of treatment. The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through **104** weeks of treatment, as well as on vasomotor symptoms	Updated to reflect extension of treatment to 104 weeks.

Section Item	Original	Amendment 2	Rationale
	such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP.	such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP.	
Section 4.2 Discussion of Study Design, Including Dosing	This open-label extension study will allow for a description of long-term efficacy data and safety for an additional ~~28~~ weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102).	This open-label extension study will allow for a description of long-term efficacy data and safety for an additional **80** weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102).	Updated timing elements to reflect extension to 80 weeks of treatment in this study.
Section 4.3.1 Exclusion Criteria	The presenting visual acuity score has decreased by ~~10~~ or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;	**11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):** **a. 90 or lower and five or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or** b. The presenting visual acuity score has decreased by **ten** or more points at the Week 24/Baseline visit relative to the parent study Baseline visit.	Clarified visual acuity criteria.
Section 4.4 Method of Assigning Patients to Treatment Group and Patient Identification Number	This extension study is a single-arm study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).	This extension study is a single-arm**, open-label** study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).	Added clarification on the open-label nature of the study.
Section 4.5 Removal of Patients from Therapy	Completion of the Week ~~52~~ visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove	Completion of the Week **104** 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	Updated to reflect extension of treatment to 104 weeks.

Section Item	Original	Amendment 2	Rationale
	patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week ~~52~~ visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).	patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week **104** visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication).	
Section 4.5 Removal of Patients from Therapy	• If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's 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 ~~of~~ eDiary completion. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;	• If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. Gross noncompliance includes < 75% compliance with the study drug over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive months) **noncompliance (**< 50% of the required number of days**) with** eDiary completion **up to Week 52 or persistent (≥ 2 eDiary collection cycles) noncompliance (< 50% of the required number of days) with eDiary completion from Week 52 to Week 104**. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;	Added clarification on timing of eDiary collection.
Section 4.6 Contraception/ Pregnancy Avoidance	Urine pregnancy tests will be performed ~~at monthly intervals during the study (~~including just prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures.	Urine pregnancy tests will be performed **according to the Schedule of Activities (Table 1-1**; including just prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. **Patients should call the investigator immediately if they suspect they may be pregnant.**	Changed for consistency so that pregnancy tests would coincide with patient visits from Week 52 to Week 104.

Section Item	Original	Amendment 2	Rationale
Section 5.1 Treatments Administered	In this extension study, all patients will receive the following open-label oral study treatment: • ~~28~~ weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate.	In this extension study, all patients will receive the following open-label oral study treatment: • **80** weeks of relugolix 40 mg tablet plus a capsule containing a tablet of 1.0 mg estradiol and 0.5 mg norethindrone acetate.	Updated timing elements to reflect extension to 80 weeks of treatment in this study.
Section 5.1 Treatments Administered	Table 5-1 Relugolix: Oral once daily/~~28~~ weeks E2/NETA: Oral once daily/~~28~~ weeks	Table 5-1 Relugolix: Oral once daily/**80** weeks E2/NETA: Oral once daily/**80** weeks	Updated timing elements to reflect extension to 80 weeks of treatment in this study.
Section 5.4 Directions for Administration	On Week 24/Baseline 1 and Week ~~52~~ clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).	On Week 24/Baseline 1**, Week 52,** and Week **104** clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).	Updated to reflect extension of treatment to 104 weeks.
Section 5.6 Storage, Packaging, and Labeling	Further guidance and information for final disposition of unused study drug are provided in the ~~Study Reference Manual and Pharmacy Manual~~.	Further guidance and information for final disposition of unused study drug are provided in the **Investigator Site File**.	Updated referenced document.
Section 5.6 Storage, Packaging, and Labeling	Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the ~~Study Reference Manual~~.	Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the **Investigator Site File**.	Updated reference document.
Section 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 Week 24/Baseline visit and Week ~~52~~/~~ET~~ visit, all used and unused study drug kits should be retained at the site. At all other visits, only used study drug kits should be retained at the site.	Patients should complete their eDiary each day on study and should bring all unused and used **(including partially used)** study drug **kits** to each study visit. At the Week 24/Baseline visit and Week **104**/**Early Termination** visit, all used**, partially used,** and unused study drug kits should be retained at the site. At all other visits, only **fully** used study drug kits should be retained at the site.	Clarified study drug accountability language and updated timing elements to reflect extension of study treatment to 104 total weeks of treatment.
Section 5.10.1 Prohibited Medications		Table 5-2 Analgesics: **Cannabinoids**	Clarification that cannabinoids are prohibited during this study.

Section Item	Original	Amendment 2	Rationale
Section 5.10.2 Permitted Medications	All concomitant medications used during the study will be recorded, including the drug generic name, dose amount, route of administration, start date, and stop date.	All concomitant medications used during the study will be recorded **in the electronic Case Report Forms (eCRFs)**, including the drug generic name, dose amount, route of administration, start date, and stop date.	Clarified where concomitant medications should be recorded.
Section 6.1 Schedule of Observations and Procedures	Further details of the procedures are provided in the ~~Study Reference Manual~~.	Further details of the procedures are provided in the **Investigator Site File**.	Updated referenced document.
Section 6.2 Open-Label Treatment Period	Open-Label Treatment Period (Week 24/Baseline to Week ~~52~~)	Open-Label Treatment Period (Week 24/Baseline to Week **104**)	Updated to reflect extension of treatment to 104 weeks.
Section 6.2 Open-Label Treatment Period		**If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.).**	Added clarification that the first dose of study drug could be initiated up to 10 days after completion of the parent study to allow for logistical issues.
Section 6.2 Open-Label Treatment Period	Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, and ~~52~~. Sites will monitor diary completion using the Trial Manager web portal throughout the study.	Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed **until Week 52. After Week 52, the eDiary will be collected on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit**. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, **52, 65, 78, 91,** and **104**. Sites will monitor diary	Updated to reflect extension of treatment to 104 weeks.

Section Item	Original	Amendment 2	Rationale
		completion using the Trial Manager web portal throughout the study. **A telephone call will be performed at Weeks 57, 71, 85 and 98. The following activities should be completed: a concomitant medication review, an evaluation of adverse events, a review of study medication compliance, a reminder of compliance with non-hormonal contraception requirements and the need to call the investigator if pregnancy is suspected, and a reminder to the patient to start recording in the eDiary daily.**	
Section 6.2 Open-Label Treatment Period	• Paper questionnaires – PGA for function – EHP Work Domain [Week24/Baseline and Week ~~52~~ only]	• Paper questionnaires – PGA for function – EHP Work Domain [Week24/Baseline**, Week 52, Week 78,** and Week **104** only]	Updated to reflect extension of treatment to 104 weeks.
Section 6.2 Open-Label Treatment Period	An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, ~~and~~ Week 52. At the Week 24/Baseline visit and Week ~~52~~ visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.	An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details**), at Week 52 for all subjects. All patients will be eligible for the Week 104 biopsy; however, patients will have the option to opt out.** Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52**, Week 65, Week 78, and Week 104.** At the Week 24/Baseline visit**, Week 52 visit,** and Week **104** visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.	Updated to include an endometrial biopsy at Week 52 and an optional endometrial biopsy at Week 104 in order to evaluate endometrial changes over the entire course of the study.

Section Item	Original	Amendment 2	Rationale
Section 6.2 Open-Label Treatment Period	Electrocardiograms will be ~~done~~ at the Week 24/Baseline and ~~at~~ the Week 52~~/Early Termination~~ visits.	Electrocardiograms will be **performed** at the Week 24/Baseline and the Week 52visits.	Updated to reflect that the last scheduled ECG for the study is planned for the Week 52 visit.
Section 6.2 Open-Label Treatment Period		Bone densitometry will occur at the Week 24/Baseline, Week 36, **Week 52,** and **Week 104**/Early Termination visits. **Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.**	Added language regarding the assessment of bone densitometry and follow-up procedures.
Section 6.3 Early Termination and Follow-up Visit	All patients withdrawing from the study prior to Week ~~52~~ will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week ~~52; however, for patients whose last dose of study drug is during Week 32 or earlier or within 4 weeks after completion of the Week 36 or Week 52 scan, the bone densitometry 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(s).	All patients withdrawing from the study prior to Week **104** will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week **104.** Bone densitometry may be performed, at the investigator's discretion, if it aids in follow-up of an ongoing adverse event(s). **Follow-up of bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.**	Clarified bone densitometry assessment at the early termination visit.
Section 6.3 Early Termination and Follow-up Visit	Patients (including those who complete the Week ~~52~~ visit and those who withdraw early from this study) will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week ~~52~~ visit, the Follow-up visit may be waived.	Patients (including those who complete the Week **104** visit and those who withdraw early from this study) will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week **104** visit, the Follow-up visit may be waived.	Updated to reflect extension of treatment to 104 weeks.

Section Item	Original	Amendment 2	Rationale
Section 6.4 Unscheduled Visits	In addition, procedures such as vital signs, weight, symptom-directed ~~brief~~ physical examination, ~~central safety~~ laboratory assessment, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed.	In addition, procedures such as vital signs, weight, **complete physical examination, sign-and** symptom-directed physical examination, **clinical** laboratory assessment, **urinalysis,** urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed.	Clarified safety assessments that could be performed at unscheduled visits.
Section 6.5.1.1 Pharmacodynamics Sample Collection	A blood sample for the pharmacodynamic analysis of serum estradiol will be collected predose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week ~~52~~ or the Early Termination visit, when no dose is administered.	A blood sample for the pharmacodynamic analysis of serum estradiol will be collected predose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week **104** or the Early Termination visit, when no dose is administered.	Updated to reflect extension of treatment to 104 weeks.
Section 6.5.1.2 Patient eDiary	All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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.	All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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 **until Week 52. After Week 52, the eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.**	Clarified timing of patient eDiary completion.
Section 6.5.2.3 Physical Examinations	A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by	A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. **The**	Clarified which physical examinations will include a breast examination.

Section Item	Original	Amendment 2	Rationale
	the patient to assess for clinically significant changes from the Baseline assessment.	**physical examinations at Week 52 and Week 104 will include a breast examination.**	
Section 6.5.2.4 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).	All protocol-required laboratory assessments must be conducted in accordance with the **Investigator Site File** and the protocol Schedule of Activities (see Section 1.1).	Updated referenced document.
Section 6.5.2.6 Bone Mineral Density	~~Patients with a bone mineral density loss of > 3% at lumbar spine or total hip at their Week 52/Early Termination visit (or most recent scan if the Week 52/ET scan was not done) relative to parent study Baseline measurement will undergo another bone densitometry scan at 6 (± 1) months and will be contacted to obtain information about medications and conditions (eg, pregnancy) that might affect bone mineral density through the time of the follow-up bone densitometry. The follow-up bone densitometry will be submitted for central reading.~~	**Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed according to the following rules:** • **For Early Termination occurring between Week 24 and Week 52:** – **For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event.** **Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.** – **For Early Termination occurring after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.** **Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was**	Added clarification for when DXA scans would be conducted and the follow-up rules for DXA results.

Section Item	Original	Amendment 2	Rationale
		> 2%, relative to the parent study baseline. **Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.** • **For Early Termination occurring between Week 52 and Week 104:** – **DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.** • **Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.** The follow-up bone densitometry will be submitted for central reading.	
Section 6.5.2.6 Bone Mineral Density	If the patient enrolls directly into another relugolix clinical study upon completion of the Week ~~52~~ visit, then the follow-up bone densitometry scan at 6 (±1) months conducted under this protocol may be waived.	If the patient enrolls directly into another relugolix clinical study upon completion of the Week **104** visit, then the follow-up bone densitometry scan at 6 (±1) months conducted under this protocol may be waived.	Updated to reflect extension of treatment to 104 weeks.
Section 6.5.2.7 Endometrial Biopsy		**For patients in parent study MVT-601-3101, an endometrial biopsy is performed at the Week 24 visit. If the required Week 24 biopsy is inadequate for diagnosis, it should be repeated, and a sample submitted to the central laboratory. If the second sample is inadequate, ensure an endometrial thickness**	With the addition of an endometrial biopsy at Week 52 and optional endometrial biopsy at Week 104, details on endometrial biopsy were added.

Section Item	Original	Amendment 2	Rationale
		has been reported from the Week 24 transvaginal ultrasound and contact the medical monitor to review the findings. Patients who have endometrial hyperplasia or endometrial carcinoma will be withdrawn from study drug treatment and followed per instructions in the parent study protocol. **Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 for all patients. At Week 104, all patients will be eligible for an additional endometrial biopsy; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.** **The Week 52 and Week 104 endometrial biopsy samples will be submitted to the central laboratory. If the Week 52 or Week 104 biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:** • **Endometrial thickness ≤ 5 mm – no further action required.** • **Endometrial thickness > 5 mm at any location or any other endometrial abnormality – repeat endometrial sampling. Contact medical monitor if second specimen is inadequate for diagnosis.**	

Section Item	Original	Amendment 2	Rationale
		Unscheduled endometrial biopsies may also be performed when medically indicated and as deemed necessary by the investigator. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy, unless urgently indicated. Additional consent is not required in this circumstance.	
Section 6.5.2.8 Status of Menstruation Recovery	If the patient enrolls directly into another relugolix clinical study upon completion of the Week ~~52~~ visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.	If the patient enrolls directly into another relugolix clinical study upon completion of the Week **104** visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.	Updated to reflect extension of treatment to 104 weeks.
Section 7.7 Study Drug Overdose Management	~~If possible, obtain a plasma sample for pharmacokinetic analysis within 2 days from the date of the last dose of study drug if requested by the medical monitor (determined on a case-by-case basis);~~		Originally included in error. Pharmacokinetic samples are not being collected for this study.
Section 7.10 Benefit/Risk Assessment	Table 7-2 Bone mineral density will be monitored at the Week 24/Baseline, Week 36, and ~~Week 52~~/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events. 12-lead ECG at the Week 24/Baseline and Week 52~~/Early Termination~~ visits, and as clinically applicable; withdrawal for QTcF > 500 msec.	Table 7-2 Bone mineral density will be monitored at the Week 24/Baseline, Week 36, **Week 52,** and **Week 104**/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events. 12-lead ECG at the Week 24/Baseline and Week 52/Early Termination visits, and as clinically applicable; withdrawal for QTcF > 500 msec.	Updated to reflect extension of treatment to 104 weeks.
Section 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	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	Updated referenced document.

Section Item	Original	Amendment 2	Rationale
	requirements, reporting of serious adverse events, and to ensure a full understanding of the ~~Study Reference Manual~~ with the site personnel.	requirements, reporting of serious adverse events, and to ensure a full understanding of the **Investigator Site File** with the site personnel.	
Section 9 Statistical Considerations and Data Analyses		**There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.**	Clarified plan to conduct two analyses (one with data through 52 weeks of treatment and one with data through 104 weeks of treatment) and develop a separate clinical study report for each analysis.
Section 9.1 Randomization Methods	This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for ~~2~~8 weeks.	This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for 8**0** weeks.	Updated timing elements to reflect extension to 80 weeks of treatment in this study.
Section 9.4 Efficacy Analyses	A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline.	A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline **in the parent study** greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline.	Clarified which baseline visit is being referred to.
Section 9.4 Efficacy Analyses	Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies. • Change from the parent study Baseline ~~to Week 52~~ in the EHP-30 Pain Domain scores; *Note: 'Week 52/EOT' were deleted from all subsequent endpoints listed.*	Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies **at Week 52 and Week 104**. • Change from the parent study Baseline to Week 52 in the EHP-30 Pain Domain scores; *Note: 'Week 52/EOT' were deleted from all subsequent endpoints listed.*	Clarified timepoints to be used in efficacy analyses.
Section 9.5 Safety Analyses	For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic)	For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic)	Updated to reflect extension of treatment, and to provide a

Section Item	Original	Amendment 2	Rationale
	mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for percent change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group.	mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for percent change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group. **The 95% CI for mean percentage change at Week 104 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104 as supportive analyses**.	description of analyses to be conducted on data from Week 104.
Section 9.5 Safety Analyses	All data will be listed and summarized by visit. The absolute change and percent change from parent study Baseline to Weeks 36 and ~~52~~ and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter.	All data will be listed and summarized by visit. The absolute change and percent change from parent study Baseline to Weeks 36**, 52,** and **104** and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter.	Updated to reflect extension of treatment to 104 weeks.
Section 9.6 Pharmacodynamics Analyses	The change from the parent study Baseline to Week 52 in pre-dose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.	The change from the parent study Baseline to Week 52 **and to Week 104** in predose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.	Updated to reflect extension of treatment to 104 weeks.
Section 9.7 Exploratory Analyses	Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint	Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint	Updated to reflect extension of treatment to 104 weeks.

Section Item	Original	Amendment 2	Rationale
	analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed: • Change from Baseline ~~to Week 52/EOT~~ in the EHP-30 scale total score; • Change from Baseline ~~to Week 52/EOT~~ in the EHP Work Domain score; • Change from parent study Baseline ~~to Week 52/EOT~~ in the EQ-5D-5L.	analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed **at Week 52 and Week 104**: • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.	
Section 9.8 Interim Analyses	~~There are no planned interim efficacy analyses.~~	**An interim analysis will be conducted at Week 52 in which all efficacy and safety endpoints will be assessed as described above. A clinical study report will be generated based on these data to support submission of 1-year data.**	Clarified plan to conduct two analyses (one with data through 52 weeks of treatment and one with data through 104 weeks of treatment) and develop a separate clinical study report for each analysis.
Section 10.1.6 Electronic Case Report Forms	For each patient enrolled, an eCRF must be completed as specified in the ~~Study Reference Manual~~.	For each patient enrolled, an eCRF must be completed as specified in the **Investigator Site File**.	Updated referenced document.
Section 10.2.3 Study Report	A clinical study report will be prepared and provided to the regulatory authority(ies).	A clinical study report will be prepared and provided to the regulatory authority(ies**) at Week 52 and a second clinical study report will be prepared at the end of the study (Week 104).**	Clarified plan to conduct two analyses (one with data through 52 weeks of treatment and one with data through 104 weeks of treatment) and develop a separate clinical study report for each analysis.

CLINICAL STUDY PROTOCOL

Study Title:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifiers:	IND No. 076642 EudraCT No. 2017-004066-10
Version and Effective Date:	Original: 06 NOV 2017 Amendment 1: 20 MAR 2018 Amendment 2: 11 Dec 2018 Amendment 3: 01 JUL 2020

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Protocol Number: MVT-601-3103 Amendment 3

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

PPD

01-Jul-2020 | 2:31 PM PDT
Date

01-Jul-2020 | 12:19 PM PDT
Date

30-Jun-2020 | 6:29 PM PDT
Date

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	novel coronavirus 2019
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dehydroepiandrosterone
DTP	direct-to-patient
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EHP	Endometriosis Health Profile
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
EU	European Union
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HR	heart rate
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NMPP	nonmenstrual pelvic pain
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change

Term	Explanation
PLD	phospholipidosis
QTc	corrected QT (interval)
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
sB&B	Subject Modified Biberoglu and Behrman
SDV	source data verification
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
ULN	upper limit of normal
US	United States
W	Week
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Protocol Number	MVT-601-3103
Location	Multinational, including North and South America, Europe, Africa, New Zealand, and Australia
Study Centers	Approximately 320 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with endometriosis-associated pain
Number of Patients Planned	Approximately 800
Study Objectives	In women with endometriosis-associated pain, the study objectives are as follows: <u>Primary Efficacy Objectives</u> To be assessed at Week 52 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. To be assessed at Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.
	<u>Secondary Efficacy Objectives</u> To be assessed at Week 52 and Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: o Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; o Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea; o Patient Global Impression of Change (PGIC) for dysmenorrhea; o Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; o Overall pelvic pain, as measured by the NRS;

	○ Analgesic use; ○ PGIC for NMPP; ○ Dyspareunia, as measured by the NRS; ○ PGIC for dyspareunia; ○ Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]); ○ 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 EHP-30 Pain Domain; ○ Patient Global Assessment (PGA) for pain; ○ PGA for function; ○ Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains; ○ Dysmenorrhea-related functional effects (sB&B); ○ NMPP-related functional effects (sB&B). <u>Safety Objectives</u> • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: ○ Adverse events; ○ Changes in bone mineral density. <u>Pharmacodynamic Objective</u> • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.
	<u>Exploratory Objective</u> • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).
Study Design The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive open-label oral relugolix 40 mg once daily co-administered with low-dose- estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Approximately	

800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 80 weeks. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, mammograms (for women ≥ 40 years of age), endometrial biopsies, and bone mineral density with DXA.

Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed according to the following rules:

- For Early Termination occurring between Week 24 and Week 52:
  - For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event.
  - Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.
  - For Early Termination occurring after Week 36, DXA is required at Early Termination unless a

DXA result is available from within six weeks prior to Early Termination.

- Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline.
- Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.

- For Early Termination occurring between Week 52 and Week 104:
  - DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.
  - Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.
- If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study drug.
- If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with parent study baseline, patients are referred to and strongly encouraged to see a bone specialist for further evaluation of the bone loss.

  Note: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan once the consultation is complete.

Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (±1) months and status of menstruation recovery, may be waived.

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.

3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable non-hormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified non-hormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study.

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;
6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia

	disorders, including Factor V Leiden; g. Migraine with aura; h. History of porphyria; 7. Has current active liver disease from any cause; 8. 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; 9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102): a. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN); or b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome); 10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug; 11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor): a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or b. The presenting visual acuity score has decreased by ten or more points at the Week 24/Baseline visit relative to the parent study Baseline visit; Note: Visual acuity score must have been obtained with corrective lenses, if applicable. 12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor; 13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).
Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.
Duration of Treatment	Study treatment will be self-administered for 80 weeks (Open-Label Treatment Period). Concomitant Medicinal Products Systematically Prescribed for All Study Patients Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug and a second-line opioid or opioid/acetaminophen or opioid/paracetamol combination for endometriosis-related pain relief as required. The specific analgesic drugs offered may differ for different countries or regions. The analgesics for each patient will be the same as those prescribed for her during the parent study.
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and Week 52, and between the parent study

	Baseline and the end of the extension study (Week 104) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study. <u>Primary Efficacy Endpoints</u> Week 52 • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. Week 104 • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores. <u>Secondary Efficacy Endpoints</u> To be assessed at Week 52 and Week 104, unless otherwise specified • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea (at Week 52 only); • Change from the parent study Baseline in the mean NMPP NRS score; • Change from the parent Baseline in the mean NRS score; • Proportion of patients not using opioids; • Proportion of patients not using analgesics; • Proportion of patients who are better or much better on the PGIC for NMPP (at Week 52 only); • Change from the parent study Baseline in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only);

	• Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline in severity scores on the PGA for pain; • Proportion of responders based on their EHP-30 Pain Domain score; • Change from the parent study Baseline in function impairment on the PGA for function; • Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B). Safety Endpoints To be assessed at Week 52 and Week 104 • Incidence of adverse events; • Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. Pharmacodynamic Endpoint To be assessed at Week 52 and Week 104 • Change from parent study Baseline in predose concentrations of serum estradiol. Exploratory Endpoints To be assessed at Week 52 and Week 104 • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.
Statistical Methods Efficacy and safety data will be analyzed using descriptive statistics by the originally randomized treatment groups. There will be no between-treatment group comparisons for the extension study data. There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis. Efficacy Efficacy data will be summarized by the original randomized treatment group assigned in the parent study (ie, Parent Study Groups A, B, and C) for the modified Intent-to-Treat Population. The analyses methods for efficacy endpoints are similar to those used for the parent studies, unless otherwise specified in the statistical analysis plan (SAP). The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated. The methods for analyzing the additional efficacy endpoints are described in the SAP.	

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52 or Week 104).

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, high level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values will be classified by toxicity grade based on the National Cancer Institute CTCAE. Laboratory shift tables of the parent study Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits. The absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change from parent study Baseline to Week 52 in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant. The 95% CI for mean percentage change at Week 104 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104 as supportive analyses.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3101 or MVT-601-3102) and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3103

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week 44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Informed Consent	X[d]											
Review Eligibility Criteria	X											
Concomitant Medications[e]	X[f]	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Weight	X[g]		X			X		X		X	X[h]	
Complete Physical Examination	X[g]					X[i]				X[j]	X[h]	
Visual Acuity[k]	X[g]											
Signs and Symptoms-Directed Physical Examination[l]		X	X	X	X		X	X	X		X[h]	X
12-Lead ECG[m]	X[g]					X				X[h]	X[h]	
Clinical Laboratory Tests[n]	X[g,o]	X	X	X	X	X[n]	X	X	X	X[n]	X[h]	X[ee]

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week 44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Pharmacodynamics Sample[p]	X[g,n]					X[n]				X[n]	X[h,n]	
Urinalysis	X[g]					X				X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Daily eDiary[q]	X[g]	X	X	X	X	X	X	X	X	X		X
Site Review of eDiary Data	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Bone Densitometry[r]	X[g]		X			X[s,t]				X[r,s]	X[h]	X[ee]
Endometrial Biopsy	X[g,u]					X				X[t]	X[h]	X[ee]
Dispense Study Treatment	X	X	X	X	X	X	X	X	X		X[h]	
Dispense or Prescribe Protocol-Specified Analgesic Drugs[v]	X	X	X	X	X	X	X	X	X		X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic	X[w]					X				X	X[h]	
Daily Self-Administration of Study Treatment[x]		X ---------- X										
Take Protocol-Specified Rescue Analgesics as Needed[y]		X ---------- X										

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week 44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
EHP-30 Questionnaire[z]	X[g]		X		X	X		X		X	X[h]	
Patient Global Assessment for Pain[y]	X[g]	X	X	X	X	X	X	X	X	X	X[h]	
[on paper] Patient Global Assessment for Function[aa]	X[g]	X	X	X	X	X	X	X	X[0]	X	X[h]	
Patient Global Impression of Change[y]	X[g]		X			X					X[h]	
[on paper] EHP Work Domain[z]	X[g]					X		X		X	X[h]	
EQ-5D-5L Questionnaire[y]	X[g]					X		X		X	X[h]	
Adverse Event Collection[bb]	X	X	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery												X[cc,ee]
Telephone Contact[dd]						X (W57)	X (W71)	X (W85)	X (W98)			
Mammogram[dd]						X[dd]				X[dd]	X[dd]	

BP = blood pressure; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; eDiary = electronic diary; EHP = Endometriosis Health Profile; EQ-5D-5L = European Quality of Life Five-Dimension Five-Level Scale; HR = heart rate; NRS = Numerical Rating Scale; PGA = Patient Global Assessment; sB&B = Subject Modified Biberoglu and Behrman; W = week.

[a] The Week 52 visit should occur on or after the 1-year anniversary of Baseline Day 1 of the parent study (± 7 days), and the Week 104 visit should occur on or after the 2-year anniversary of Baseline Day 1 of the parent study.

[b] Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.

[c] The Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit.

[d] May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3103 is defined by administration of the first dose of MVT-601-3103 study drug.

[e] Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up Period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3103 should be reported as concomitant medications in the parent study (MVT-601-3101 or MVT-601-3102). If concomitant medication is ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.

[f] Concomitant medications are recorded both for the parent study and for MVT-601-3103 at the Week 24/Baseline visit. (See footnote e for further details).

[g] This is a parent study (MVT-601-3101 or MVT-601-3102) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3103 and is covered under the informed consent for the parent study.

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

[i] The Week 52 and Week 104 physical examinations will include a breast examination.

[j] See parent study protocols (MVT-601-3101 or MVT-601-3102) for instructions on testing visual acuity.

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

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

[m] Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, Week 91, and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests will include the following: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.

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

[o] For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week 104/Early Termination, collect a sample for analysis of estradiol concentrations only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are collected.

[p] All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study. 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 until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.

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

[r] See Section 6.5.2.6 for details on the timing and follow-up of bone densitometry.

[s] Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed based on the timing of the Early Termination visit. For Early Termination occurring after Week 24 and before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event, and follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. For Early Termination occurring after Week 36 and before Week 52, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2% or most recent DXA result was after Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. For Early Termination occurring between Week 52 and Week 104, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.

[t] Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details) and at Week 52 and Early Termination visit for all patients. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension; however, patients will have the option to opt out.

[u] Please see Appendix 1 for list of protocol-specified analgesics and see the Investigator Site File for information on where and how to obtain protocol-specified analgesic medications by country. At the Week 104 visit, patients who will not be proceeding to another 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 another extension study, refer to the protocol for that next study.

[v] Pregnancy test must be negative before the study drug dose is administered. For patients whose Baseline Day 1 visit is conducted on a different day than the parent study Week 24 visit, perform an unscheduled pregnancy test at Baseline Day 1 prior to administering the first dose of study drug.

[w] Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). If necessary, for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week 104/Early Termination visit.

[x] Patients may only take their study-specified analgesics for pain. Analgesics should not be taken prophylactically (ie, in anticipation of pain).

[y] The patient will enter her response(s) into an electronic 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.

[z] The patient will enter her response onto a paper questionnaire at the site. Paper questionnaires should be done in the following order: PGA for function, EHP Work Domain.

[aa] Collect adverse events from the time that the first dose of study drug for MVT-601-3103 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3103 should be reported as an adverse event in the parent study (MVT-601-3101 or MVT-601-3102). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.

[bb] Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted 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. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

[cc] A telephone call will be performed at Weeks 57, 71, 85, and 98. The following activities should be completed: a concomitant medication review, evaluation of adverse events, and a review of eDiary and study medication compliance.

[dd] For patients ≥ 40 years old at the time of the Week 52 visit, Week 104 visit, or Early Termination visit only. See Section 6.5.2.9.

[ee] See Section 6.5.2.6, Section 6.5.2.7, and Section 6.5.2.8 to determine if additional follow-up is required.

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 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

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

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once-daily oral medication for the treatment of 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 was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

3. STUDY OBJECTIVES AND ENDPOINTS

Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and Week 52, and between the parent study Baseline the end of the extension study (Week 104) for the following parent study treatment groups:

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

The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study.

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

Objectives	Endpoints
Primary Efficacy	
To be assessed at Week 52 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. To be assessed at Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	To be assessed at Week 52 • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. To be assessed at Week 104 • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores.
Secondary Efficacy	
To be assessed at Week 52 and Week 104 To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: • Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; • Dysmenorrhea, as measured by the NRS for dysmenorrhea; • Patient Global Impression of Change (PGIC) for dysmenorrhea;	To be assessed at Week 52 and Week 104, unless otherwise specified • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea (at Week 52 only);

Objectives	Endpoints
• NMPP, as measured by the NRS for NMPP;	• Change from the parent study Baseline in the mean NMPP NRS score;
• Overall pelvic pain, as measured by the NRS	• Change from the parent Baseline in the mean NRS score;
• Analgesic use	• Proportion of patients not using opioids; • Proportion of patients not using analgesics;
• PGIC for NMPP	• Proportion of patients who are better or much better on the PGIC for NMPP (at Week 52 only);
• Dyspareunia, as measured by the NRS;	• Change from the parent study Baseline in the mean dyspareunia NRS scores;
• PGIC for dyspareunia;	• Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only);
• Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]);	• Change from the parent study Baseline 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 function measured by the EHP-30 Pain Domain;	• Proportion of responders based on EHP-30 Pain Domain scores;
• Patient Global Assessment (PGA) for pain;	• Change from the parent study Baseline in severity scores on the PGA for pain;
• PGA for function;	• Change from the parent study Baseline in function impairment on the PGA for function;
• Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains;	• Change from the parent study in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
• Dysmenorrhea-related functional effects (sB&B);	• Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B);
• NMPP-related functional effects (sB&B).	• Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).
Safety	
To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	To be assessed at Week 52 and Week 104

Objectives	Endpoints
• Adverse events; • Changes in bone mineral density.	• Incidence of adverse events; • Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	To be assessed at Week 52 and Week 104 • Change from parent study Baseline in predose concentrations of serum estradiol.
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	To be assessed at Week 52 and Week 104 • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive open-label oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 80 weeks. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open-label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed

during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, mammograms (for women ≥ 40 years of age), endometrial biopsies, and bone mineral density with DXA.

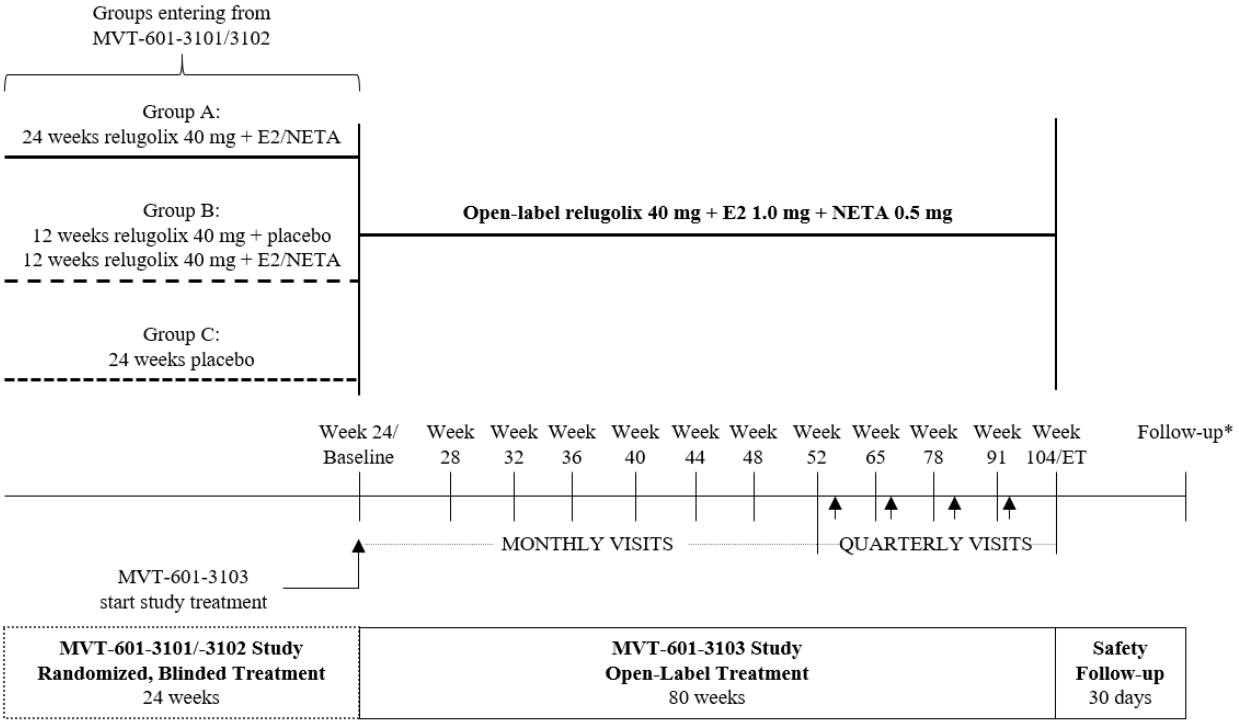
At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via DXA. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.

Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed (or is ongoing) 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 will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 (± 1) months and status of menstruation recover, may be waived.

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

Figure 4-1 MVT-601-3103 Study Schematic



E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; eDiary = electronic diary; ET = Early Termination.
* The Follow-up visit is schedule approximately 30 days after the last dose of study drug.
↑ Indicates telephone contact to review concomitant medication, evaluation of adverse events, and a review of eDiary and study medication compliance. To be conducted at Week 57, Week 71, Week 85, and Week 98.

4.2. Discussion of Study Design, Including Dosing

The SPIRIT EXTENSION study (MVT-601-3103) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3101 and MVT-601-3102) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with endometriosis-associated pain. This 80-week extension study provides additional efficacy and safety data up to 104 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of

the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40-mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 104 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 104 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2017; Lee, 2016; Franke, 2000] or endometriosis-associated pain [Wu, 2014]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the United States (US) as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that

lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3101 and MVT-601-3102) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a significant decrease in endometriosis-associated pain in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose estradiol and norethindrone acetate to decrease dysmenorrhea and NMPP and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 80 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102). This study design will allow eligible patients with endometriosis-associated pain, including those randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 800 premenopausal women aged 18 to 51 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. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.

3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable non-hormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified non-hormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;

6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or
    b. The presenting visual acuity score has decreased by ten or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.

12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor;
13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).

4.4. Method of Assigning Patients to Treatment Group and Patient Identification Number

Eligible patients who sign consent will be identified with the same Patient Identification (ID) Number assigned to the patient during the parent study. This extension study is a single-arm, open-label study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).

4.5. Removal of Patients from Therapy

Completion of the Week 104 visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 104 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication). When patients complete the study or early terminate from the study, they must be deactivated from the study in the interactive voice response system/interactive web response system (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 enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 x ULN; or
  - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);

- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. Gross noncompliance includes < 75% compliance with the study drug over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive months) noncompliance (< 50% of the required number of days) with eDiary completion up to Week 52 or persistent (≥ 2 eDiary collection cycles) noncompliance (< 50% of the required number of days) with eDiary completion from Week 52 to Week 104. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting);
- Evidence of malignant breast lesion(s) or breast carcinoma on Week 52 or Week 104/Early Termination or most recent mammogram or additional breast imaging (see Section 6.5.2.9 for more information on mammogram at Week 52 or Week 104/Early Termination);

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

4.6. Contraception/Pregnancy Avoidance

All patients should be counseled at every visit to adhere to the use of protocol allowed contraceptive methods. In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study including through 30 days following the last dose of study drug, unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure) at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;

- Has a non-hormonal intrauterine device (eg, Paragard) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

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

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

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

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

Urine pregnancy tests will be performed according to the Schedule of Activities (Table 1-1; including just prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

4.7. Novel Coronavirus 2019 Guidance

Guidance for conducting clinical trials during the novel coronavirus 2019 (COVID-19) pandemic is included in Appendix 9.

5. TREATMENTS

5.1. Treatments Administered

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

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

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

Table 5-2 Description of MVT-601-3103 Study Drugs

Name of Investigational Product	Relugolix	Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material
Dosage Form	Tablet	Capsule
Unit Dose Strength	40 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily/ 80 weeks	Oral once daily/ 80 weeks

Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug (NSAID) and a second-line opioid or opioid/acetaminophen (or paracetamol) 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 1. 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 common excipients.

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

5.3. Randomization and Stratification

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

5.4. Directions for Administration

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

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

On Week 24/Baseline 1, Week 52, and Week 104 clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. 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. Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Investigator Site File. 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 lot/batch 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 and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the Investigator Site File.

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. The study-specified pain medications for each patient will be the same as for the parent study. Only study-specific Tier 1 and Tier 2 analgesic medications (see Appendix 1) should be taken starting with the Baseline/Week 24 visit and subsequently. Analgesic medications will be taken for control of pain and not prophylactically.

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 when appropriate.

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 at the time of enrollment into this study. 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 the time of enrollment in this study, 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 eDiary.

5.8. Blinding

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

5.9. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and should bring all unused and used (including partially used) study drug kits to each study visit. At the Week 24/Baseline visit and

Week 104/Early Termination visit, all used, partially used, and unused study drug kits should be retained at the site. At all other visits, only fully used study drug kits should be retained at the site. New study drug should be dispensed as described in Section 1.1 (Schedule of Activities).

Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Because of the importance to both safety and efficacy evaluation, patients who are grossly noncompliant with eDiary completion must undergo an Unscheduled visit to evaluate reasons for noncompliance 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 4.5 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. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 5-2 are prohibited at any time during the study through the Follow-Up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-3 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	
GnRH analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-androgens	danazol	
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	Note: All other anticonvulsants are allowed
Aromatase inhibitors	anastrozole letrozole	

Drug Class	Examples	Comments
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective estrogen receptor modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective progesterone receptor modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products “natural” thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine devices	levonorgestrel	
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.

Drug Class	Examples	Comments
P-glycoprotein inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir[f]	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.
Moderate and strong P-glycoprotein- inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	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.
Analgesic drugs **other** than those specified for use during the study[h]	Acetaminophen/paracetamol (other than any included in a study-specified analgesic) aspirin > 325 mg/day NSAIDs (other than study-specified NSAIDs) gabapentin pregabalin carbamazepine metamizole cannabinoids	Note: Aspirin ≤ 325 mg per day is allowed

Drug Class	Examples	Comments
Antidepressants New treatment or changed doses of SSRI, SNRI, or TCA antidepressants	**SNRI examples:** duloxetine venlafaxine desvenlafaxine **SSRI examples:** citalopram fluoxetine paroxetine fluvoxamine **TCA examples:** amitriptyline doxepin desipramine nortriptyline	SSRI, SNRI, or TCA allowed if given at the same dose as used during the 3 months prior to the Run-In Period of MVT-601-3101 or MVT-601-3102. 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.

DHEA = dihydroepiandrosterone; GnRH = gonadotropin-releasing hormone; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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.
h. For situations where non-study analgesics may be allowed, see Section 5.7.

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded in the electronic Case Report Forms (eCRFs), including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

All analgesics will be collected in the eDiary and recorded in the eCRFs.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of endometriosis is prohibited from the Week 24/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File. Guidelines to address the COVID-19 pandemic are included in Appendix 9.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 2 periods: Open-Label Treatment Period and Safety Follow-Up Period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3101 or MVT-601-3102 will serve as the Week 24/Baseline procedures for patients who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

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

- Informed consent (unless signed previously);
- Record concomitant medications;
- Update the patient's status in the IVRS/IWRS as being in the MVT-601-3103 and receive the lot numbers for study drug allocation;
- Dispense study treatment;
- Dispense or prescribe protocol-specified analgesic drugs;
- Transition the patient within her eDiary from the parent study to MVT-601-3103
- Take study drug dose in clinic; and
- Record adverse events, if any.

The Week 24 visit date in the parent study is defined as the date that the last procedures for the Week 24 visit were completed, acknowledging that the Week 24 visit procedures may be completed on different dates. Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and

with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.).

Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed until Week 52. After Week 52, the eDiary will be collected on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, 52, 65, 78, 91, and 104. Sites will monitor diary completion using the Trial Manager web portal throughout the study.

A telephone call will be performed at Weeks 57, 71, 85 and 98. The following activities should be completed: a concomitant medication review, an evaluation of adverse events, a review of study medication compliance, and a reminder to the patient to start recording in the eDiary daily.

Accountability for study drug will be performed at each visit. Instructions for analgesic medication usage will be reinforced at each visit.

Questionnaires are administered on the electronic tablet and on paper at each visit. These procedures should occur before any other types of study procedures are performed. When both electronic tablet and paper questionnaires are required at a visit, 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 function
  - EHP Work Domain [Week24/Baseline, Week 52, Week 78, and Week 104 only]

Patients will bring their eDiary, analgesic medications, and study drug to each visit. The site must document the start and stop dates of the patient's menses.

An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details). An endometrial biopsy is required at Week 52 and the Early Termination visit for all patients. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension ; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, Week 91, and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.

Electrocardiograms will be performed at the Week 24/Baseline and the Week 52 visits.

A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study (see Section 6.5.2.9).

Bone densitometry will occur at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.

Bone densitometry and ECGs will be submitted for central reading.

Study drug compliance will be reviewed at each visit. Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

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

6.3. Early Termination Visit and Follow-up Visit

All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event.. Bone densitometry may be performed at the investigator's discretion, if it aids in follow-up of an ongoing adverse event(s). Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.

Patients (including those who complete the Week 104 visit and those who withdraw early from this study) will have a Follow-up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week 104 visit, the Follow-up visit may be waived.

The Follow-up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (see Section 1.1) for individual study visit procedures during the Follow-up visit.

Follow-up of bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.

6.4. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source

documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, mammogram (for women ≥ 40 years old), 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Pharmacodynamics Sample Collection

A blood sample for the pharmacodynamic analysis of serum estradiol will be collected predose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week 104 or the Early Termination visit, when no dose is administered. These pharmacodynamic samples will be analyzed at a central laboratory. These results will not be shared with the sites at any time.

6.5.1.2. Patient eDiary

All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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 until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.

The site should review the eDiary data at every visit.

6.5.1.3. 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 3). Patients will complete the EHP-30 questionnaire at the site at visits indicated in Section 1.1 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.

6.5.1.4. 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 4). 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 visits indicated in Section 1.1 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.

6.5.1.5. 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 5) 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. The PGA for pain severity and the PGIC will be completed on a tablet device at the study site. The PGA for function will be completed on a paper questionnaire at the study site.

6.5.1.6. 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 6). Patients will complete the EHP Work Domain questionnaire at visits indicated in Section 1.1 before other types of study procedures, such as blood draws and physical examinations, are performed. The EHP Work Domain will be completed on a paper questionnaire at the study site.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

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

6.5.2.2. Vital Signs

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

6.5.2.3. Physical Examinations

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. The physical examinations at Week 52 and Week 104 will include a breast examination.

6.5.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Investigator Site File 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 6-4 Clinical Laboratory Tests

Chemistry	Hematology	Urinalysis
Potassium Chloride Bicarbonate Blood urea nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Creatine kinase Hemoglobin A1c Bilirubin total Alanine aminotransferase Aspartate aminotransferase Gamma-glutamyl transferase Alkaline phosphatase	White blood cell count White blood cell differential Red blood cell count Hemoglobin Hematocrit Mean corpuscular volume Platelet count Red blood cell morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine microscopy (reflex testing based on abnormal urine analysis)
Hormones	**Lipids**	**Pregnancy**
Estradiol	Total cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, 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.

For patients with incomplete recovery of bone mineral density loss at the 6- and 12-month post-treatment follow-up visit, clinical laboratory tests should be performed (see Section 6.5.2.6).

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

6.5.2.5. Electrocardiograms

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

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3, and L4), total hip, and femoral neck (same leg within each patient) at the time points described in the Schedule of Activities (Section 1.1). The scan will be read by the central imaging laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory ad described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will be used at each site and operated in the same scan mode for all scans for an individual patient and should be the same as used for the patient during the parent study (MVT-601-3101 and MVT-601-3102). The central core imaging laboratory will collect and evaluate all DXA scan for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study.

Determination of bone mineral density by DXA at early termination and follow-up of findings will proceed according to the following rules:

- For early termination occurring between Week 24 and Week 52:
  - For early termination occurring before Week 36, DXA is not required at the Early Termination visit unless it will aid in the assessment of an adverse event;

    Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline;
  - For early termination occurring after Week 36, DXA is required at early termination unless a DXA result is available from within six weeks prior to early termination;

    Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline;
  - Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline;
- For early termination occurring between Week 52 and Week 104:

– DXA is required at early termination unless a DXA result is available from within six weeks prior to early termination;

Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to the parent study baseline;

- If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study drug. Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous).
- If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with parent study baseline, patients are referred to and strongly encouraged to see a bone specialist for further evaluation or the bone loss. Patients undergoing 12-month post-treatment follow-up should also have the following clinical laboratory evaluations (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous).

Note: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan once the consultation is complete.

6.5.2.7. Endometrial Biopsy

For patients in parent study MVT-601-3101, an endometrial biopsy is performed at the Week 24 visit. If the required Week 24 biopsy is inadequate for diagnosis, it should be repeated, and a sample submitted to the central laboratory. If the second sample is inadequate, ensure an endometrial thickness has been reported from the Week 24 transvaginal ultrasound and contact the medical monitor to review the findings. Patients who have endometrial hyperplasia or endometrial carcinoma will be withdrawn from study drug treatment and followed per instructions in the parent study protocol.

Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 and Early Termination visit for all patients. An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.

The Week 52, Week 104, and Early Termination visit endometrial biopsy samples will be submitted to the central laboratory. If the Week 52,Week 104, or Early Termination visit biopsy

specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:

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

Investigators should contact the medical monitor if a patient refuses to have an endometrial biopsy at Week 52 or the Early Termination visit.Unscheduled endometrial biopsies may also be performed when medically indicated and as deemed necessary by the investigator. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy, unless urgently indicated. Additional consent is not required in this circumstance.

6.5.2.8. Status of Menstruation Recovery

If the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

6.5.2.9. Mammogram

A mammogram will be performed at Week 52 or Week 104/Early Termination visit (see the Schedule of Activities in Section 1.1) for patients ≥ 40 years of age at the time of the visit. If a patient had a recent mammogram per standard of care within the six months before Week 52 that was Breast Imaging Reporting and Data System category 1 or 2 or equivalent or had benign findings, as determined by the investigator or medical monitor, a mammogram is not required at Week 52 but should be completed by Week 104/Early Termination. If a patient turns 40 years old after the Week 52 visit has occurred, a mammogram should be performed no later than the Week 104/Early Termination visit.

All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 8) and recorded in the eCRF. The following actions will be taken depending on the reading:

- Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;

- Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;
- Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours.

7. SAFETY CONSIDERATIONS

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

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 admitted to a hospital, independent of the duration of that hospitalization. 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 and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor regardless of causal relationship to study drug treatment.

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

7.3. Assigning Causal Relationship to Study Drug

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

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

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 7-5 Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute CTCAE

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

CTCAE = Common Terminology Criteria for Adverse Events.

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 × ULN.

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

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

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

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

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

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

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

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 × ULN; AND
2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:

– Hepatobiliary tract disease;

– Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);

- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
- Alcoholic hepatitis;
- Nonalcoholic steatohepatitis;
- Autoimmune hepatitis.

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

7.6. Serious Adverse Event Reporting

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

The contact information for submission of serious adverse events, adverse events of clinical interest (defined in Section 7.5), and events of overdose is available on the Safety 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-601-3103);
- 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 within 24 hours;
- 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 safety report 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.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy 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 form, as available. Document the pregnancy in the eCRF as well.

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

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

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on 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 (corrected QT [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD), reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

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

Table 7-6 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the parent studies.	Bone mineral density will be monitored at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the parent studies.	12-lead ECG at the Week 24/Baseline and Week 52visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 x the ULN; total bilirubin values > 1.5 x ULN	Abnormal liver test results (AST or ALT > 3 x ULN) that develop during the Open-Label Treatment Period will be reported within 24 hours of study personnel awareness.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.

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) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 24/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each study visit; A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study, with specified discontinuation criteria. Adverse events will be recorded

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; QTc = corrected QT interval; QTcF = QT interval by the Fridericia correction; PLD = phospholipidosis; ULN = upper limit of normal.

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 Investigator Site File 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 (SAP) will describe the detailed statistical methods and analyses for this study.

All efficacy and safety measures over the course of both the parent and extension studies will be presented by the parent study treatment group using descriptive statistics. No formal treatment comparisons will be performed for this extension study. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.

9.1. Randomization Methods

This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for 80 weeks.

9.2. Analysis Populations

Efficacy data analyses will be performed on the Modified Intent-to-Treat (mITT) Population, defined as all patients who were randomized in a parent study (MVT-601-3101 or MVT-601-3102) and who have received any amount of randomized study drug.

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

The analysis methods for safety and efficacy endpoints are the same as those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Justification

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

9.4. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the mITT Population.

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

The point estimates and 2-sided 95% confidence intervals (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline in the parent study greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline. Patients who had a pain reduction less than the pre-determined threshold or who had an increase in the use of analgesics for endometriosis-associated pain will be considered non-responders. The pain reduction thresholds will be determined for NMPP and dysmenorrhea separately (see the SAP for details) for the parent studies and these same thresholds will be applied to this study.

Baseline values are calculated using the Baseline pain assessment period, which is defined as the period from the date of the first dose of placebo in the parent study Run-In Period through the day prior to the first dose of randomized study drug. Patients' average NRS pain scores and use of rescue analgesic medications for endometriosis-associated pain (dysmenorrhea or NMPP) will be compared between a given visit-specific pain assessment period (eg, Week 28, Week 32, etc.) and the Baseline pain assessment period. The visit-specific pain assessment period is defined as the last 35 calendar days immediately prior to and including the last dose of study drug treatment received prior to the visit date.

For any pain assessment period (Baseline or visit-specific), the average NRS scores will be calculated for dysmenorrhea and NMPP separately. An average NRS score for dysmenorrhea is calculated as the average NRS score over the days with menses during a given pain assessment period. An average NRS score for NMPP is calculated as the average NRS score over the days without menses during a given pain assessment period. The analgesic use for a given pain assessment period is summarized by total dose count defined as the average daily dose count taken during the given pain assessment period multiplied by 35. Additional details on calculating dose counts and on the precise definition of an increase in analgesic use will be provided in the SAP.

Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies at Week 52 and Week 104.

- Change from the parent study Baseline in the EHP-30 Pain Domain scores;
- Change from the parent study Baseline to in the mean dysmenorrhea NRS score;
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea;
- Change from the parent study Baseline in the mean NMPP NRS score;
- Change from the parent Baseline in the mean NRS score;
- Proportion of patients not using opioids;
- Proportion of patients not using analgesics;
- Proportion of patients who are better or much better on the PGIC for NMPP;
- Change from the parent study Baseline in the mean dyspareunia NRS scores;
- Proportion of patients who are better or much better on the PGIC for dyspareunia;

- Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale;
- Change from the parent study Baseline in severity scores on the PGA for pain;
- Proportion of responders based on EHP-30 Pain Domain scores;
- Change from the parent study Baseline in function impairment on the PGA for function;
- Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
- Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B);
- Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).

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

For endpoint of proportion of responders based on EHP-30 Pain Domain scores, a responder is defined using the same within-patient score change threshold determined from the parent studies.

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, mammograms (women ≥ 40 years of age), and endometrial biopsy. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.

The treatment-emergent period will be defined as the period of time from the first dose date and time of randomized study drug in the parent study 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, 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, high level term, and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

Laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. The National Cancer Institute CTCAE will be used to categorize toxicity grade for the laboratory parameters. Shift tables will be provided

for each gradable parameter to summarize baseline toxicity grade versus post-baseline toxicity grade. For laboratory parameters that are not gradable by the CTCAE, a shift table based upon the normal range (low, normal, and high) will be provided for each parameter to summarize the parent study Baseline versus post-baseline results. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by parent study treatment group for each laboratory test.

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

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. Electrocardiograms will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic) mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for percent change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group. The 95% CI for mean percentage change at Week 104 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104 as supportive analyses.

All data will be listed and summarized by visit. The absolute change and percent change from parent study Baseline to Weeks 36, 52, and 104 and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the parent study treatment group.

Additional analyses will be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Pharmacodynamics Analyses

The change from the parent study Baseline to Week 52 and to Week 104 in predose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.

9.7. Exploratory Analyses

Descriptive summaries by treatment group and between treatment group comparisons (when applicable) will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed at Week 52 and Week 104:

- Change from Baseline in the EHP-30 scale total score;
- Change from Baseline in the EHP Work Domain score;
- Change from parent study Baseline in the EQ-5D-5L.

9.8. Interim Analyses

An interim analysis will be conducted at Week 52 in which all efficacy and safety endpoints will be assessed as described above. A clinical study report will be generated based on these data to support submission of one-year data.

9.9. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

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

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

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

signed and dated by the patient 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, US, 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 Investigator Site File. 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 lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, accountability, and returned or destroyed study

product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient 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, European Union (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. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

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

10.2.3. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies) at Week 52 and a second clinical study report will be prepared at the end of the study (Week 104). 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). 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.

11. REFERENCES

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12. APPENDICES

Appendix 1. 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)
- Tier 2[1]
  - 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).

Appendix 2. Daily eDiary

Version 3 MY80005-eDiary
US English Screen Report 23May2017

Screen report: my80005-eDiary Subject Facing

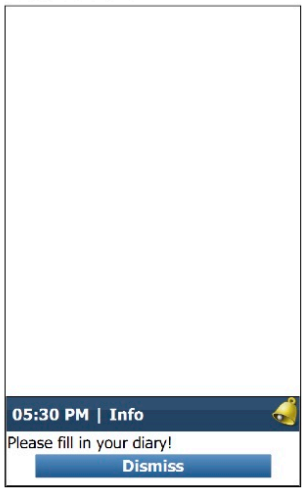
Localized texts are displayed in English.

Contents

Version 3
US English Screen Report

MY80005-eDiary
23May2017

1 Common



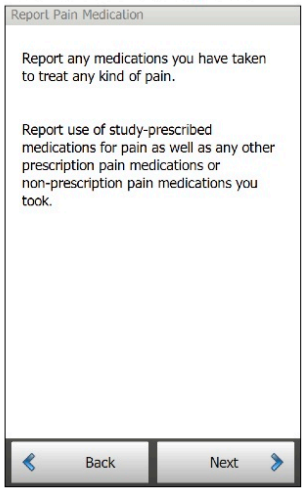
Message 1

Note: Time will populate per device

Version 3
US English Screen Report

MY80005-eDiary
23May2017

2 Form: MedReport



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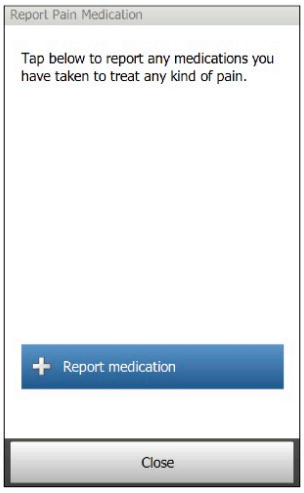

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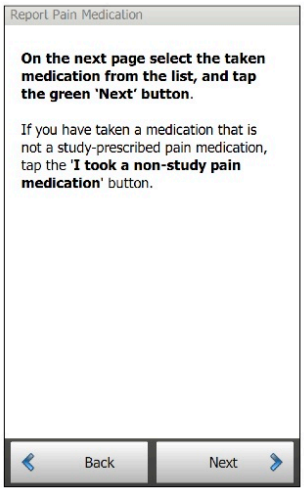

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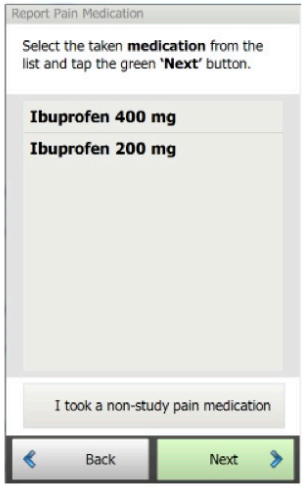

Screen 4

Note: Medications will show per patient set up

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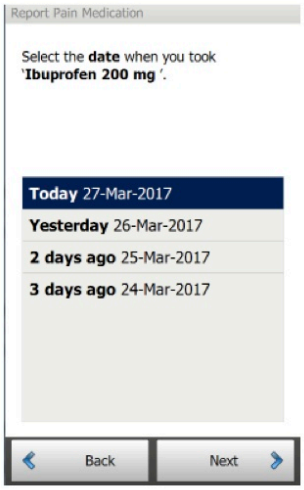


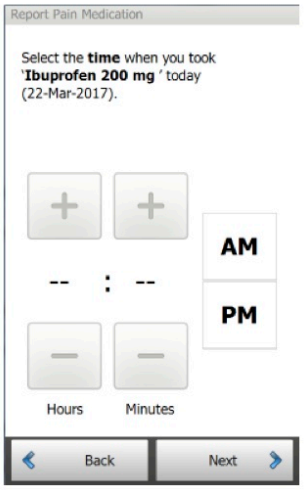
Screen 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2

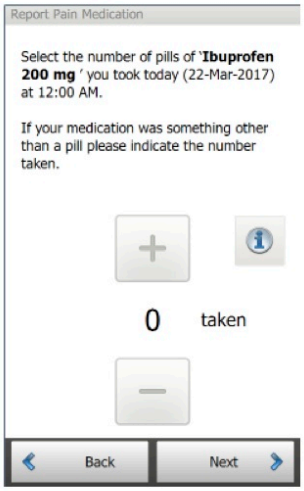


Screen 6

Message 3

Note: Medication Name and Date will show per device

Message 4



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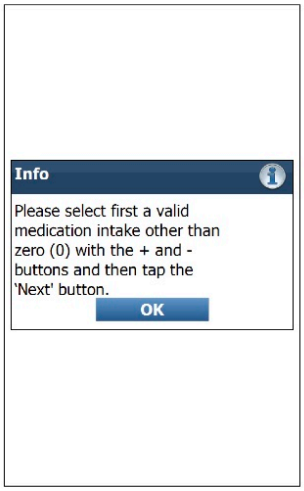

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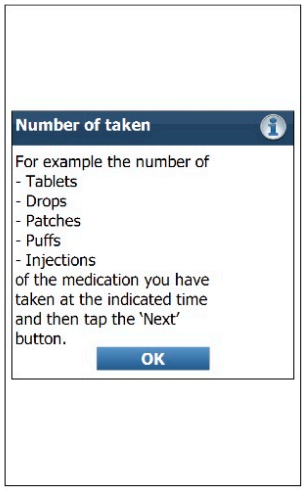
Note: Medication Name and Date and time will show per device

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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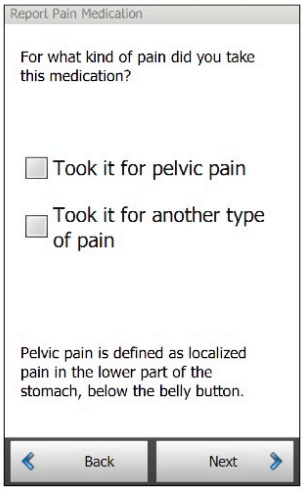

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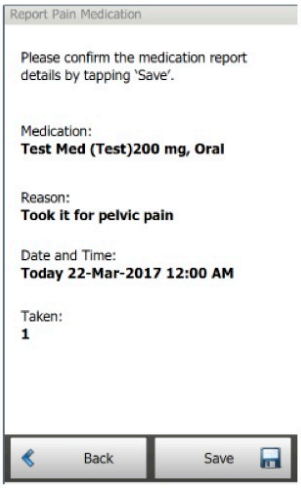
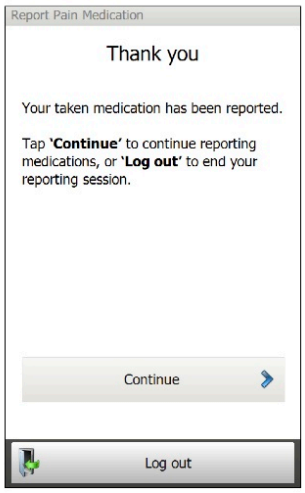


Screen 9

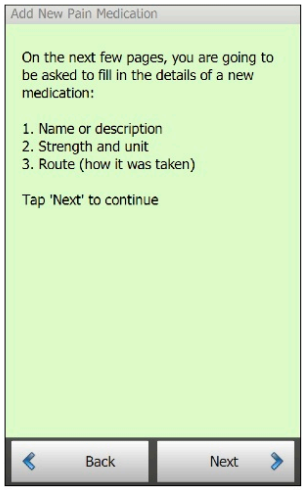
Note: 'Medication', 'Reason', 'Date and Time', 'Taken' will show per patient selection



Screen 10

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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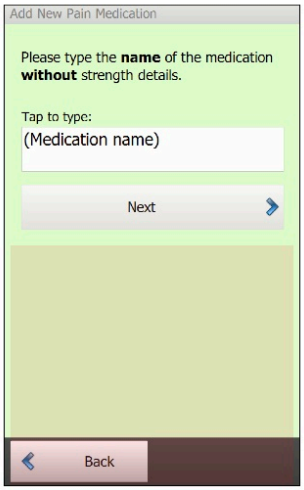

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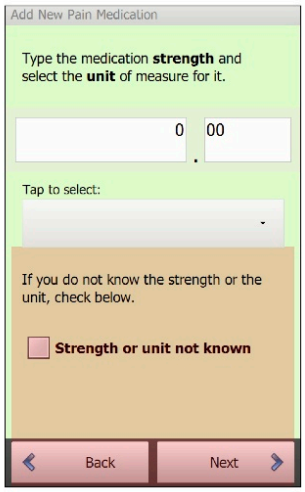

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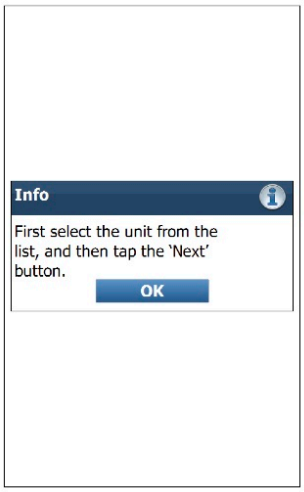
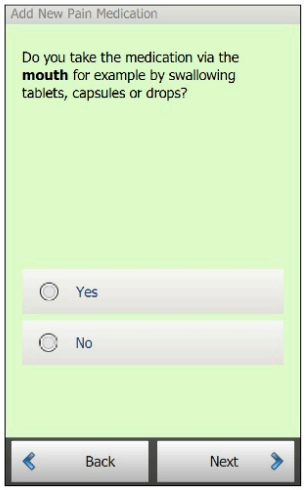


Message 9

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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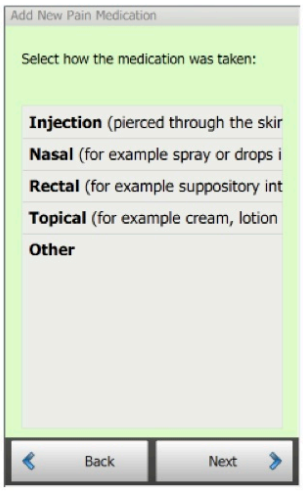

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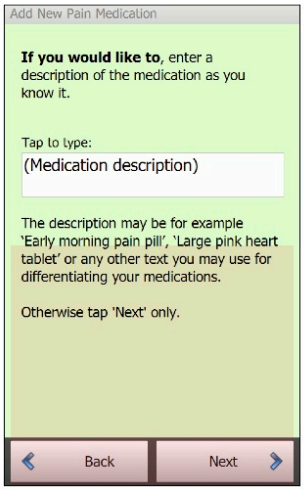

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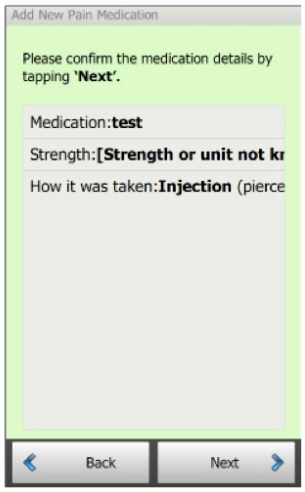
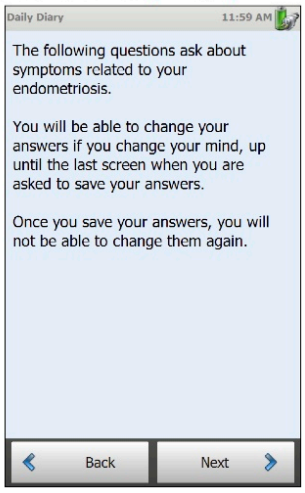


Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

3 Form: Daily Diary



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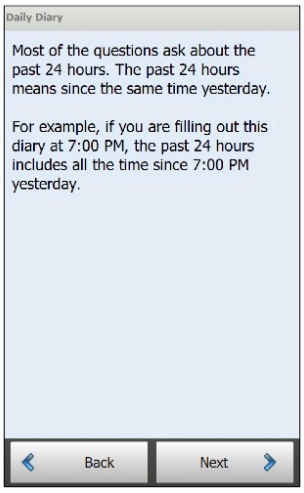

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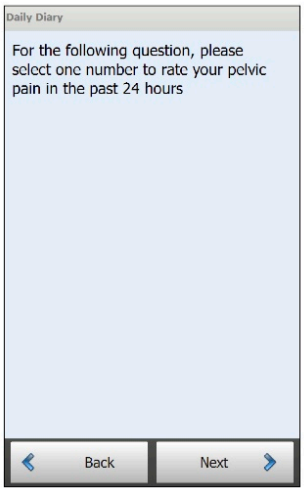

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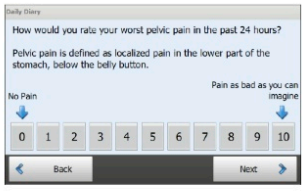

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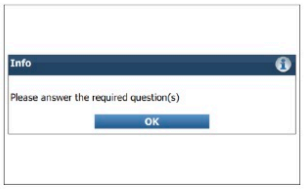

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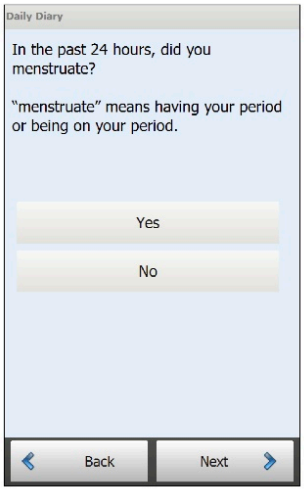
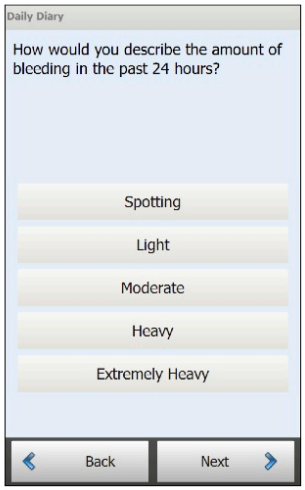


Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017



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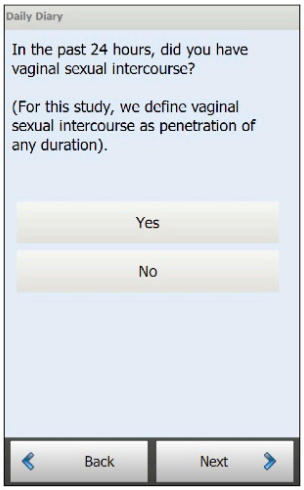

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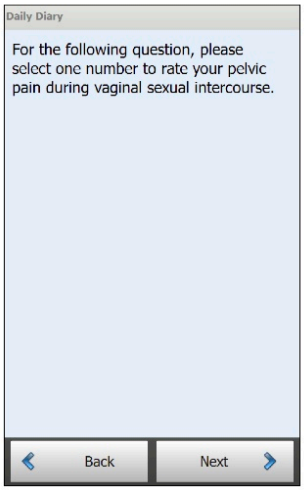

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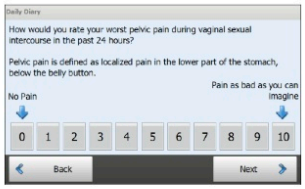
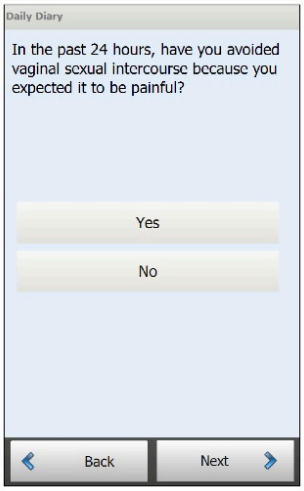
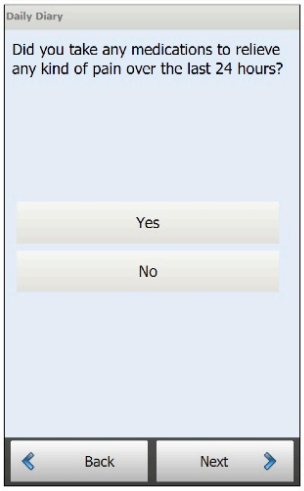


Screen 9

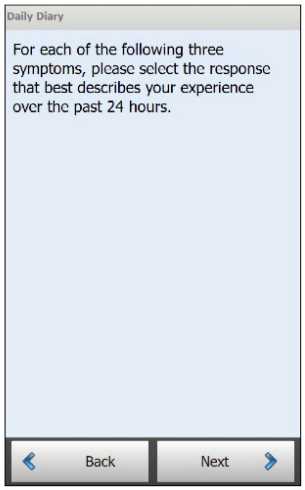


Screen 10

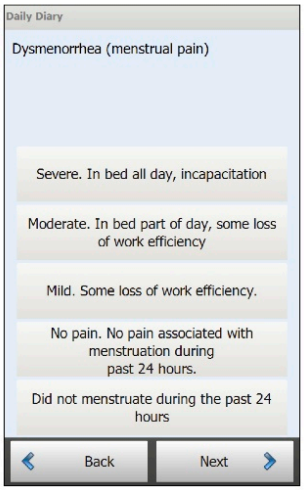


Screen 11

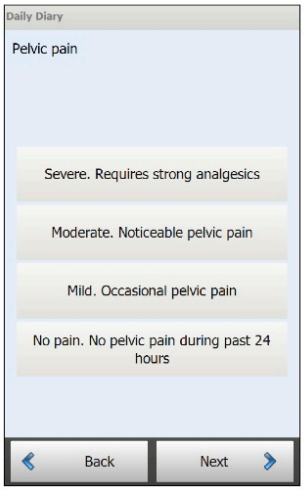
Version 3 MY80005-eDiary
US English Screen Report 23May2017



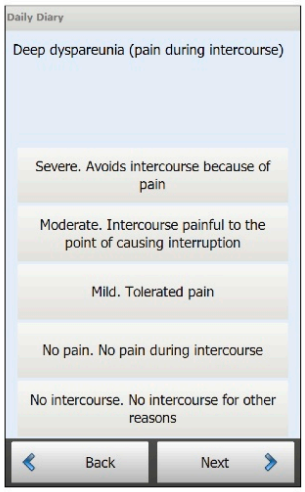
Screen 12



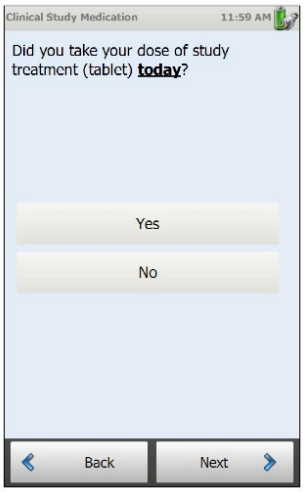
Screen 13



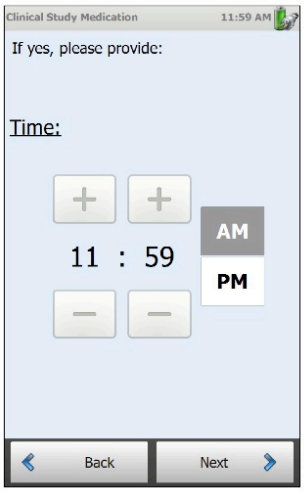
Screen 14



Screen 15



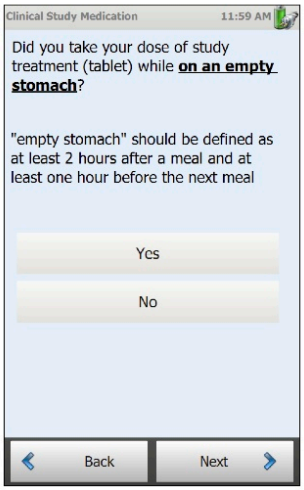
Screen 16



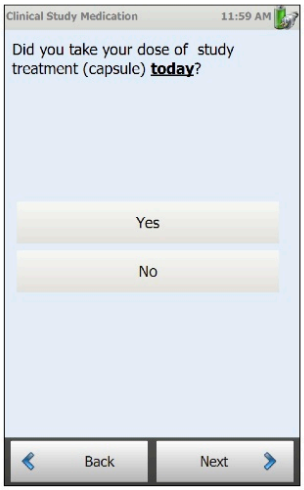
Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

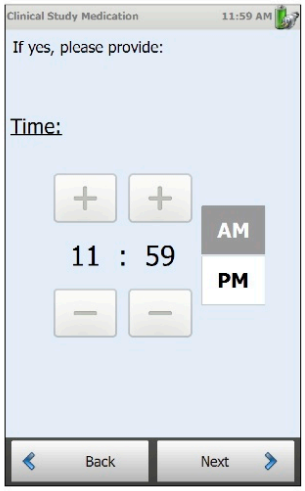
Message 2



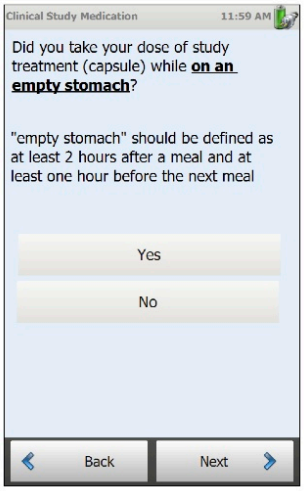
Screen 18



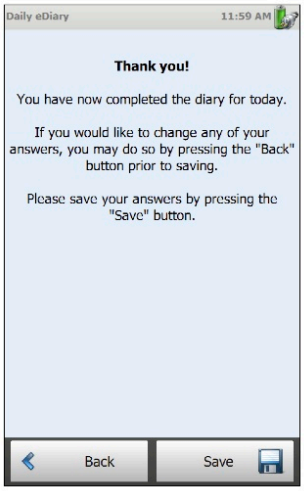
Screen 19



Screen 20



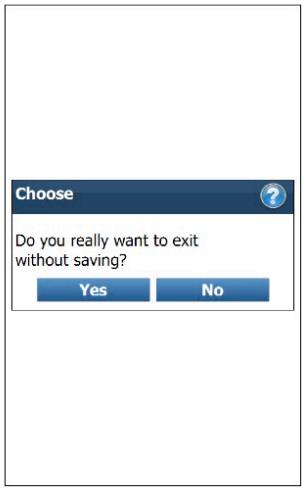
Screen 21



Screen 22

Version 3
US English Screen Report

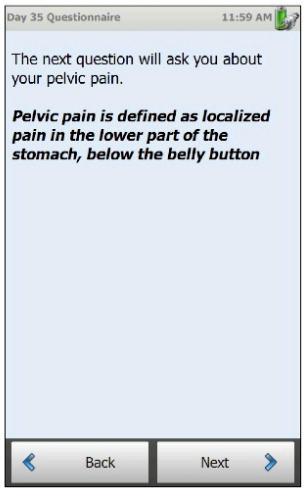
MY80005-eDiary
23May2017



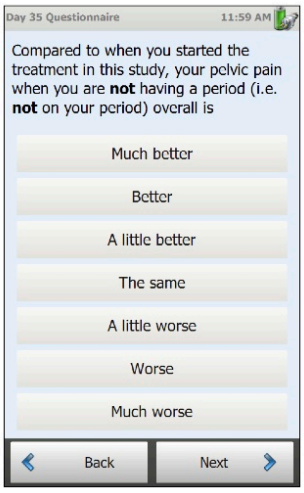
Message 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

4 Form: PGIC-NMPP

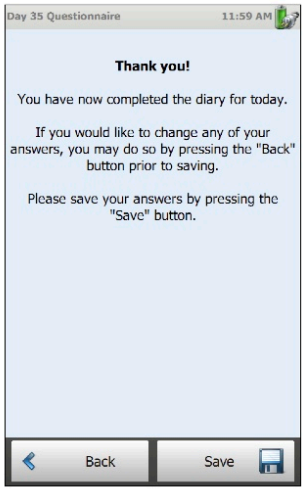


Screen 1

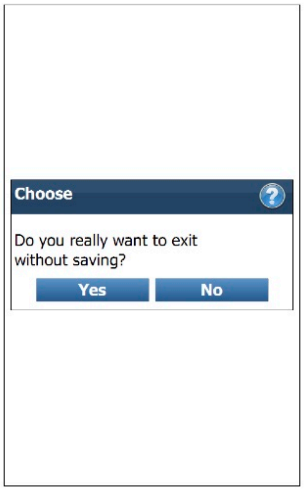


Screen 2

Message 1



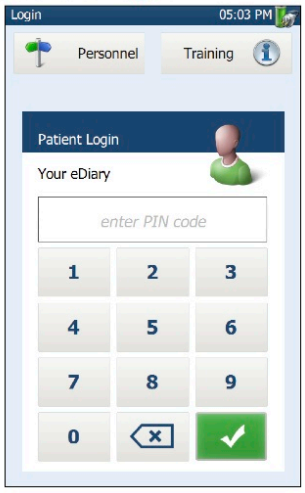
Screen 3



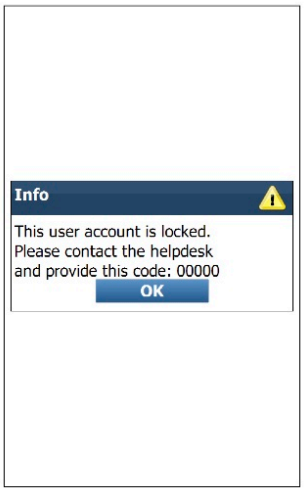
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

5 Form: Login



Screen 1

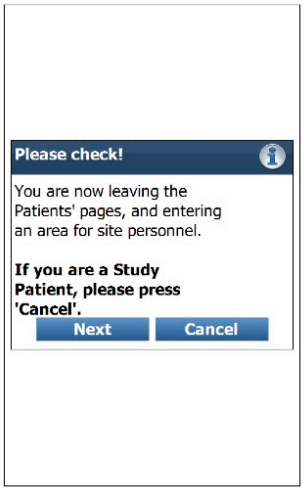


Message 1

Message 2

Message 3

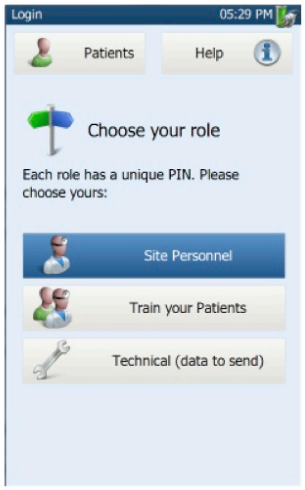
Message 4



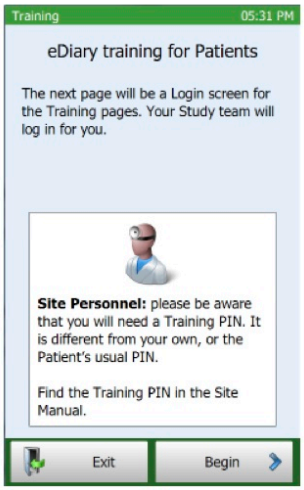
Message 5

Version 3
US English Screen Report

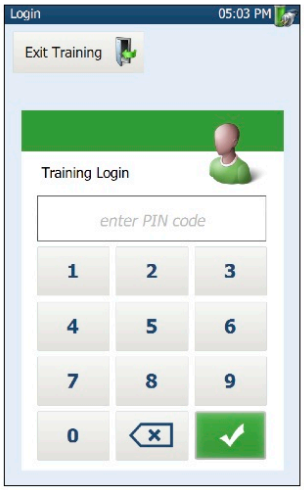
MY80005-eDiary
23May2017



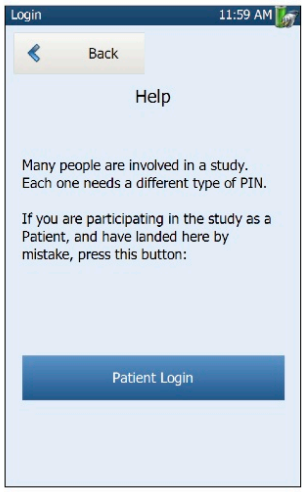
Screen 2



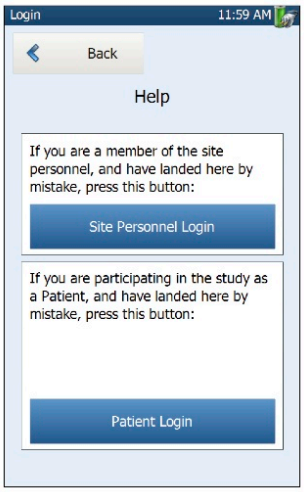
Screen 3



Screen 4



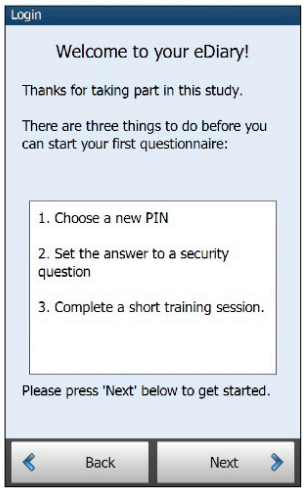
Screen 5



Screen 6

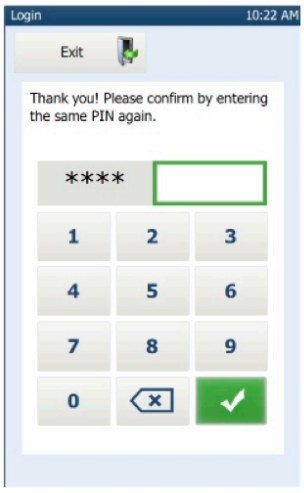
Version 3 MY80005-eDiary
US English Screen Report 23May2017

6 Form: PIN change



Screen 1

Screen 2



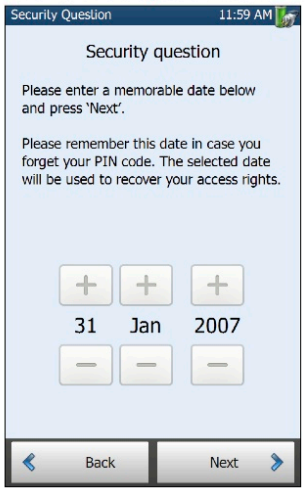
Screen 3

Message 1

Version 3
US English Screen Report

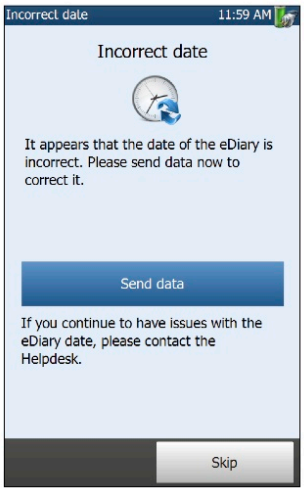
MY80005-eDiary
23May2017

7 Form: Subject main menu

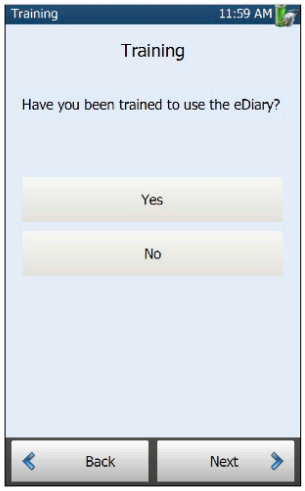


Screen 1

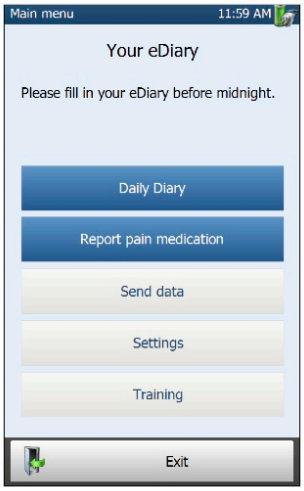
Message 1



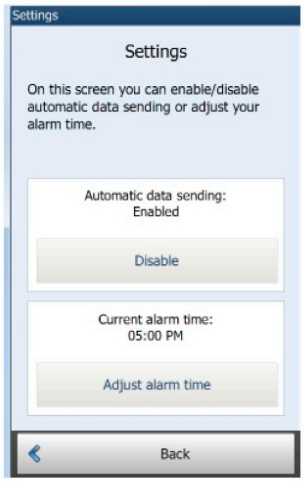
Screen 2



Screen 3



Screen 4



Screen 5

Note: Time will update per device

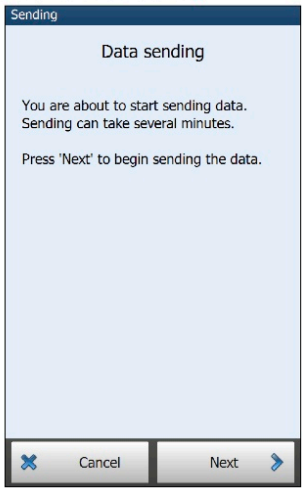
Version 3
US English Screen Report

MY80005-eDiary
23May2017

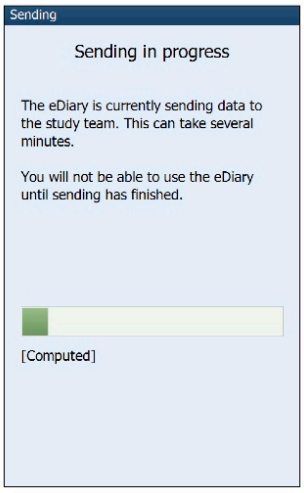
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

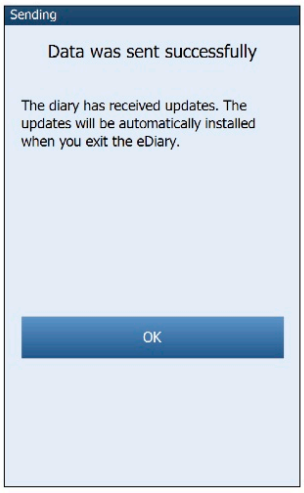
8 Form: Sending



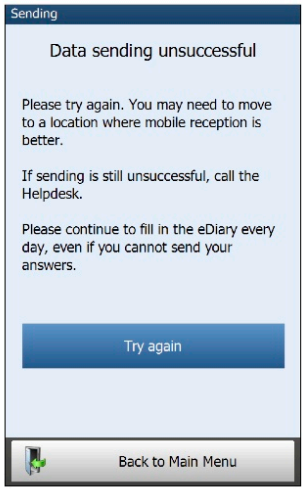
Screen 1



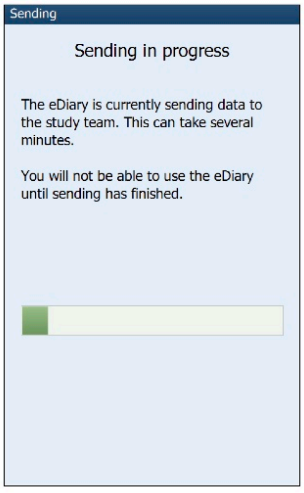
Screen 2



Screen 3



Screen 4

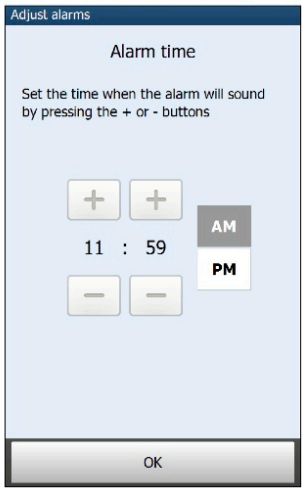


Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017

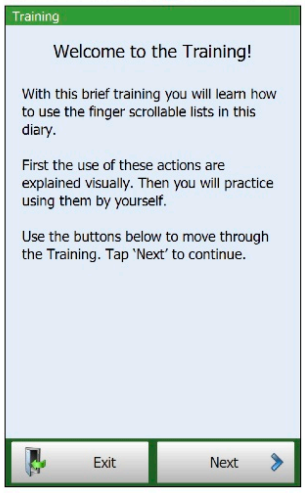
9 Form: AlarmSetup



Screen 1

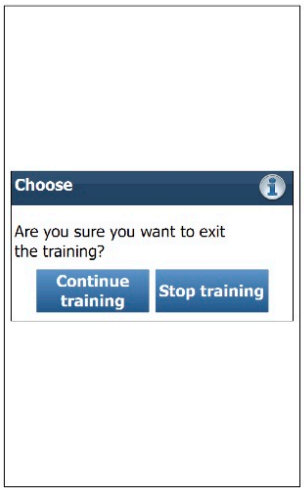
Version 3 MY80005-eDiary
US English Screen Report 23May2017

10 Form: Subject training diary

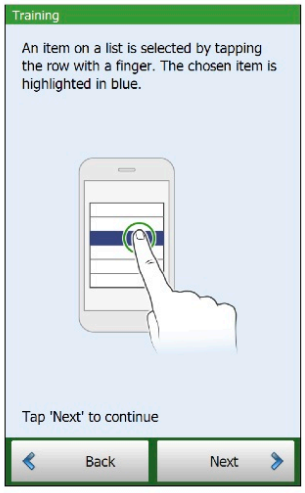


Screen 1

Message 1

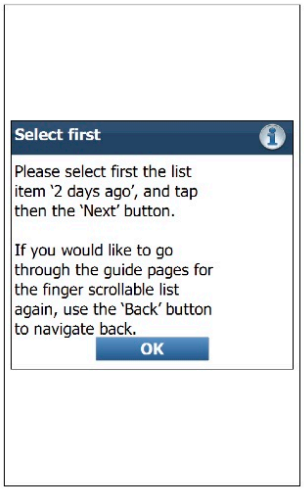


Message 2



Screen 2

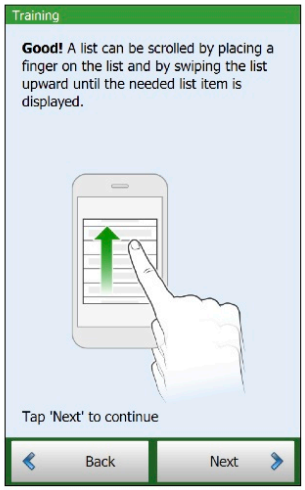
Screen 3



Message 3

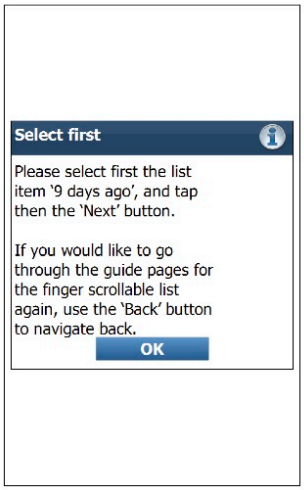
Version 3
US English Screen Report

MY80005-eDiary
23May2017

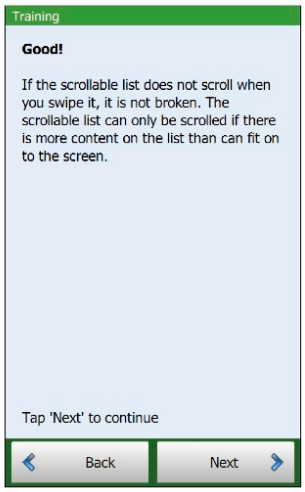


Screen 4

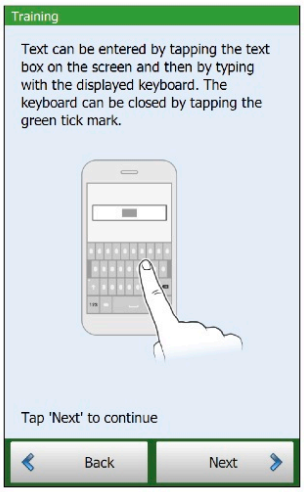
Screen 5



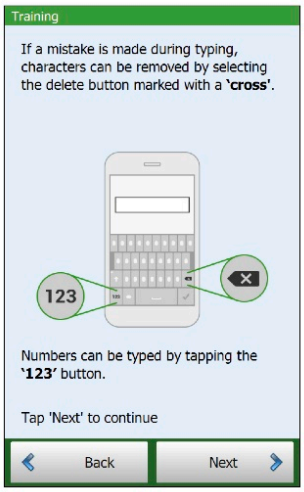
Message 4



Screen 6



Screen 7



Screen 8

Version 3
US English Screen Report

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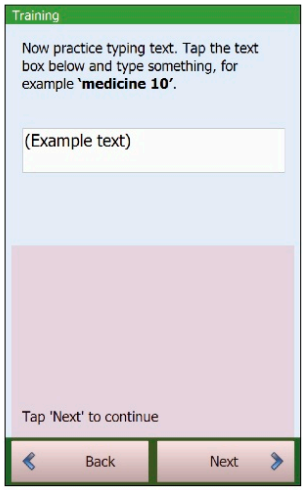
23May2017



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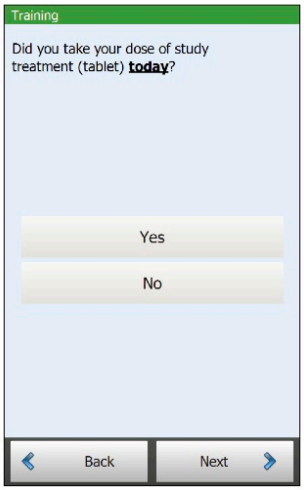
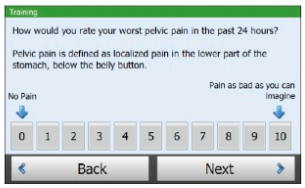


Screen 10

Message 5



Screen 11

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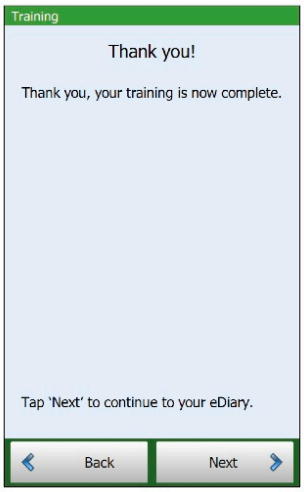

Screen 12

Version 3
US English Screen Report

MY80005-eDiary
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11 Keyboards

Appendix 3. 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.		☐	☐	☐	☐	☐
2.		☐	☐	☐	☐	☐
3.		☐	☐	☐	☐	☐
4.		☐	☐	☐	☐	☐
5.		☐	☐	☐	☐	☐
6.		☐	☐	☐	☐	☐

Checked one box for each question

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

	Never	Rarely	Sometimes	Often	Always
7.	☐	☐	☐	☐	☐
8.	☐	☐	☐	☐	☐
9.	☐	☐	☐	☐	☐
10.	☐	☐	☐	☐	☐
11.	☐	☐	☐	☐	☐
12.	☐	☐	☐	☐	☐
13.	☐	☐	☐	☐	☐
14.	☐	☐	☐	☐	☐

Checked one box for each question

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

	Never	Rarely	Sometimes	Often	Always
15.	☐	☐	☐	☐	☐
16.	☐	☐	☐	☐	☐
17.	☐	☐	☐	☐	☐
18.	☐	☐	☐	☐	☐
19.	☐	☐	☐	☐	☐
20.	☐	☐	☐	☐	☐
21.	☐	☐	☐	☐	☐
22.	☐	☐	☐	☐	☐

Checked one box for each question

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

	Never	Rarely	Sometimes	Often	Always
23.	☐	☐	☐	☐	☐
24.	☐	☐	☐	☐	☐
25.	☐	☐	☐	☐	☐
26.	☐	☐	☐	☐	☐
27.	☐	☐	☐	☐	☐
28.	☐	☐	☐	☐	☐
29.	☐	☐	☐	☐	☐
30.	☐	☐	☐	☐	☐

Check one box for each question.

Appendix 4. 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 ❑

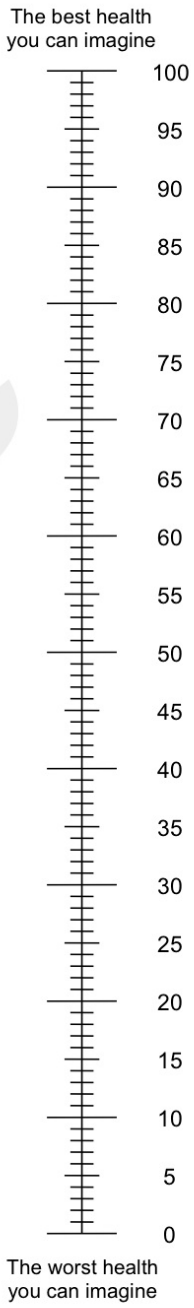
ANXIETY / DEPRESSION

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 5. 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

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

- Not at all
- Minimally
- Moderately
- Significantly
- Very significantly

Note: PGA for function is administered via a paper questionnaire.

Appendix 6. Endometriosis Health Profile - Work Domain

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: EHP Work Domain is administered via a paper questionnaire.

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

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

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

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

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

Recommended tests:

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

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

CBC = complete blood count; INR = international normalized ratio.

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. 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 9. Guidance for Study Conduct during the COVID-19 Pandemic

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

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

Safety During the COVID-19 Pandemic

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

Protocol Adherence

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

Visit Schedules and Study Procedures

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

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, in the earliest allowable portion of the visit window, taking all measures to prevent contracting COVID-19.

- All protocol required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, Investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.

- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the Myovant medical monitor for consultation as necessary.

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

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

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

As soon as the study patients are able to return to the investigational site for an on-site visit, they should return either for their next scheduled visit (if still within protocol window) or for an unscheduled visit (if outside of expected protocol visit window).

Study Participant Study Drug Supply

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

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

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

Onsite Study Monitoring Restrictions

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

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

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

- FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated June 03, 2020);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (28 April 2020).

AMENDMENT 3: SUMMARY OF CHANGES

The MVT-601-3103 clinical study protocol has been amended as described in the table below. The primary purpose of the amendment is to include a mammogram at Week 52 or Week 104/Early Termination for women ≥ 40 years old.

A detailed list of changes is described below, where deleted text is indicated by ~~strikethrough~~ and new text is indicated with **bold** formatting. Note that the correction of typos, minor clarifications, and minor wording changes to improve readability, understanding, and consistency may not be included in this table.

Section Item	Original	Amendment 3	Rationale
Title Page	Amendment 2: 11 Dec 2018	Amendment 2: 11 Dec 2018 **Amendment 3: 01 JUL 2020**	Added current version and date.
Sponsor Signature Page	Protocol Number: MVT-601-3103 Amendment ~~2~~	Protocol Number: MVT-601-3103 Amendment **3**	Updated amendment number.
List of Abbreviations		**COVID-19 novel coronavirus 2019**	Added new abbreviation.
List of Abbreviations		**DTP direct-to-patient**	Added new abbreviation.
List of Abbreviations		**SDV source data verification**	Added new abbreviation.
1. Synopsis Secondary Efficacy Objectives	• Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; • PGIC for NMPP;	• Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; • **Overall pelvic pain, as measured by the NRS;** • **Analgesic use;** • PGIC for NMPP;	Included additional objectives to evaluate pelvic pain and analgesic use.
1. Synopsis Secondary Efficacy Endpoints		• **Change from the parent Baseline in the mean NRS score;** • **Proportion of patients not using opioids;** • **Proportion of patients not using analgesics;**	Included additional endpoints to evaluate pelvic pain and analgesic use.
1. Synopsis Study Design	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density with DXA.	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, **mammograms (for women ≥ 40 years of age), endometrial biopsies,** and bone mineral density with DXA.	Added mammogram for patients over 40 years age.
1. Synopsis Study Design		• **If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months**	Clarified follow-up procedures for bone mineral density loss.

Section Item	Original	Amendment 3	Rationale
		from the date of the last dose of the study drug. • **If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with parent study baseline, patients are referred to and strongly encouraged to see a bone specialist for further evaluation of the bone loss.** **Note: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan once achieved.**	
1. Synopsis Study Design	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.**	Clarified procedures for when a patient is lost to follow-up.
1.1. Schedule of Activities 12-Lead ECG Week 104/Early Termination		**X[h]**	Added ECG at Week 104/Early Termination visit.

Section Item	Original	Amendment 3	Rationale
1.1. Schedule of Activities Clinical Laboratory Tests during Safety Follow-up		**X[ee]**	Added clinical laboratory tests during follow-up period since they may be included as part of bone densitometry follow-up.
1.1. Schedule of Activities Bone Densitometry during Safety Follow-up		**X[ee]**	Added bone densitometry follow-up.
1.1. Schedule of Activities Endometrial Biopsy during Safety Follow-up		**X[ee]**	Added endometrial biopsy follow-up.
1.1. Schedule of Activities Status of Menstruation Recovery during Safety Follow-up	X[bb]	X[bb,ee]	Added clarifying footnote for status of menstruation recovery during safety follow-up.
1.1. Schedule of Activities		**Mammogram at Week 52, Week 104/Early Termination, and Unscheduled** **X[dd]**	Added mammogram for patients over 40 years age.
1.1. Schedule of Activities Footnote r	~~This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within 4 weeks after completion of the Week 36 or Week 52 scan. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.~~	**See Section 6.5.2.6 for details on the timing and follow-up of bone densitometry.**	Clarified bone densitometry follow-up.
1.1. Schedule of Activities Footnote t	Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study	Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study	Clarified endometrial biopsy procedures.

Section Item	Original	Amendment 3	Rationale
	Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details)~~,~~ at Week 52 for all patients. ~~All~~ patients ~~are eligible for a biopsy at Week 104~~; however, patients will have the option to opt out.	Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details) **and** at Week 52 **and Early Termination visit** for all patients. **This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all** patients **who complete the open-label extension**; however, patients will have the option to opt out.	
1.1. Schedule of Activities Footnote bb	Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.	Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted 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. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.**	Clarified procedures for when a patient is lost-follow-up.
1.1. Schedule of Activities Footnote dd		**For patients ≥ 40 years old at the time of the Week 52 visit, Week 104 visit, or Early Termination visit only. See Section 6.5.2.9.**	Added clarification on timing of mammograms.
1.1. Schedule of Activities Footnote ee		**See Section 6.5.2.6, Section 6.5.2.7, and Section 6.5.2.8 to determine if additional follow-up is required.**	Add cross-references for additional information on safety follow-up.
3. Study Objectives and Endpoints		Objectives • **Overall pelvic pain, as measured by the NRS;** • **Analgesic use;**	Included additional objectives and corresponding endpoints to evaluate pelvic pain and analgesic use.

Section Item	Original	Amendment 3	Rationale
		Endpoints • **Change from the parent Baseline in the mean NRS score;** • **Proportion of patients not using opioids;** • **Proportion of patients not using analgesics;**	
4.1. Overall Study Design	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density with DXA.	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, **mammograms (for women ≥ 40 years of age), endometrial biopsies,** and bone mineral density with DXA.	Added mammogram for patients over 40 years age.
4.1. Overall Study Design	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.**	Clarified procedures for when a patient is lost to follow-up.
4.5. Removal of Patients from Therapy		**Evidence of malignant breast lesion(s) or breast carcinoma on Week 52 or Week 104/Early Termination or most recent mammogram or additional breast imaging (see Section 6.5.2.9 for more information on mammogram at Week 52 or Week 104/Early Termination);**	Included removal criteria for findings resulting from mammogram.
4.6. Contraception /Pregnancy Avoidance	In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal	**All patients should be counseled at every visit to adhere to the use of protocol allowed contraceptive methods.** In this study,	Added language for increased counselling on contraception.

Section Item	Original	Amendment 3	Rationale
	contraception throughout the study including through 30 days following the last dose of study drug, unless any of the following apply:	medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study including through 30 days following the last dose of study drug, unless any of the following apply:	
4.7. Novel Coronavirus 2019 Guidance		**Guidance for conducting clinical trials during the novel coronavirus 2019 (COVID-19) pandemic is included in Appendix 9.**	Included COVID-19 guidance.
5.1. Treatments Administered Table 5-1	Description of MVT-601-~~3003~~ Study Drugs	Description of MVT-601-**3103** Study Drugs	Corrected study number.
5.10.1. Prohibited Medications Table 5-2	Intrauterine devices: levonorgestrel ~~copper~~	Intrauterine devices: levonorgestrel	Removed copper to reduce confusion with inclusion criterion 6c.
6. Study Assessments and Procedures	The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File.	The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File. **Guidelines to address the COVID-19 pandemic are included in Appendix 9.**	Included COVID-19 guidance.
6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)	An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details), ~~at~~ Week 52 for all ~~subjects~~. ~~All patients will be eligible for the Week 104 biopsy~~; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104	An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details)**. An endometrial biopsy is required at** Week 52 **and the Early Termination visit** for all **patients**. **This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete**	Clarified endometrial biopsy timing.

Section Item	Original	Amendment 3	Rationale
	visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.	**the open-label extension**; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78**, Week 91,** and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.	
6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)		**A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study (see Section** 6.5.2.9).	Added mammogram for patients over 40 years age.
6.3. Early Termination Visit and Follow-up Visit	All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. Bone densitometry may be performed at the investigator's discretion, if it aids in follow-up of an ongoing adverse event(s). Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.	All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. **An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event.** Bone densitometry may be performed at the investigator's discretion, if it aids in follow-up of an ongoing adverse event(s). Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.	Clarified endometrial biopsy timing.
6.4. Unscheduled Visits	Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the	Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the	Added mammogram for patients over 40 years age.

Section Item	Original	Amendment 3	Rationale
	patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.	patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, **mammogram (for women ≥ 40 years old),** 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.	
6.5.2.4. Clinical Laboratory Tests		**For patients with incomplete recovery of bone mineral density loss at the 6- and 12-month post-treatment follow-up visit, clinical laboratory tests should be performed (see Section 6.5.2.6).**	Included clinical laboratory evaluations associated with bone densitometry follow-up.
6.5.2.6. Bone Mineral Density		• **If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study**	Clarified follow-up procedures for bone mineral density loss.

Section Item	Original	Amendment 3	Rationale
		drug. Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous). • **If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with parent study baseline, patients are referred to and strongly encouraged to see a bone specialist for further evaluation of the bone loss. Patients undergoing 12-month post-treatment follow-up should also have the following clinical laboratory evaluations (vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous).** **Note: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan once achieved.**	
6.5.2.7. Endometrial Biopsy	Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 for all patients. ~~At Week 104, all patients will be eligible for an additional endometrial biopsy~~; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study.	Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 **and Early Termination visit** for all patients. **An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the**	Clarified endometrial biopsy timing.

Section Item	Original	Amendment 3	Rationale
	The Week 52 ~~and~~ Week 104 endometrial biopsy samples will be submitted to the central laboratory. If the Week 52 ~~or~~ Week 104 biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:	**endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension**; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study. The Week 52**,** Week 104**, and Early Termination visit** endometrial biopsy samples will be submitted to the central laboratory. If the Week 52**,** Week 104**, or Early Termination visit** biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:	
6.5.2.7. Endometrial Biopsy		**Investigators should contact the medical monitor if a patient refuses to have an endometrial biopsy at Week 52 or the Early Termination visit.**	Clarified investigator role in communicating to sponsor when a patient refuses the endometrial biopsy.
6.5.2.8. Status of Menstruation Recovery	If the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.	If the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to**	Clarified procedures for when a patient is lost to follow-up.

Section Item	Original	Amendment 3	Rationale
		contact the patient by telephone, a certified letter must be sent to the patient.	
6.5.2.9. Mammogram		**A mammogram will be performed at Week 52 or Week 104/Early Termination visit (see the Schedule of Activities in Section 1.1) for patients ≥ 40 years of age at the time of the visit. If a patient had a recent mammogram per standard of care within the six months before Week 52 that was Breast Imaging Reporting and Data System category 1 or 2 or equivalent or had benign findings, as determined by the investigator or medical monitor, a mammogram is not required at Week 52 but should be completed by Week 104/Early Termination. If a patient turns 40 years old after the Week 52 visit has occurred, a mammogram should be performed no later than the Week 104/Early Termination visit. All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 8) and recorded in the eCRF. The following actions will be taken depending on the reading:** • **Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;** • **Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;** • **Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours.**	Added mammogram for patients over 40 years age.

Section Item	Original	Amendment 3	Rationale
7.2.1. Adverse Event Reporting Period	Adverse events and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor ~~if the investigator assesses the event as related to the study drug treatment~~.	Adverse events and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor **regardless of causal relationship to study drug treatment**.	Clarified reporting instructions.
7.7. Study Drug Overdose Management	Contact the medical monitor ~~immediately~~;	Contact the medical monitor **within 24 hours**;	Clarified timing of overdose reporting requirements.
7.8. Pregnancy Reporting	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 form, as available.	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 form, as available. **Document the pregnancy in the eCRF as well.**	Added clarification about the documentation of pregnancy.
Section 7.10 Table 7-2	<u>Monitoring and Withdrawal Criteria</u> Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.	<u>Monitoring and Withdrawal Criteria</u> Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each **study** visit**;** **A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the**	Added details to correspond with the addition of mammaograms.

Section Item	Original	Amendment 3	Rationale
		study, with specified discontinuation criteria. Adverse events will be recorded	
9.4. Efficacy Analyses		• **Change from the parent Baseline in the mean NRS score;** • **Proportion of patients not using opioids;** • **Proportion of patients not using analgesics;**	Included additional endpoints to evaluate pelvic pain and analgesic use.
9.5 Safety Analyses	Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, ~~and~~ bone mineral density with DXA. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.	Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA**, mammograms (women ≥ 40 years of age), and endometrial biopsy**. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.	Included added assessments.
Appendix 8		Added appendix.	Corresponding information for the addition of mammograms.
Appendix 9		Added appendix.	Details regarding the conduct of clinical trials during the COVID-19 pandemic.

CLINICAL STUDY PROTOCOL

Study Title:	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Investigational Product:	Relugolix
Protocol Number:	MVT-601-3103
Indication:	Treatment of Endometriosis-Associated Pain
Sponsor:	Myovant Sciences GmbH Viaduktstrasse 8 4051 Basel Switzerland
Regulatory Identifiers:	IND No. 076642 EudraCT No. 2017-004066-10
Version and Effective Date:	Original: 06 NOV 2017 Amendment 1: 20 MAR 2018 Amendment 2: 11 Dec 2018 Amendment 3.1: 25 Aug 2020

CONFIDENTIALITY STATEMENT

SPONSOR SIGNATURE PAGE

SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain

Protocol Number: MVT-601-3103 Amendment 3.1

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

PPD

25-Aug-2020 | 3:15 PM PDT

Date

PPD

PPD

25-Aug-2020 | 11:42 AM PDT

Date

PPD

PPD

PPD

25-Aug-2020 | 12:23 PM PDT

Date

PPD

PPD

INVESTIGATOR STATEMENT

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

Principal Investigator Name (Printed)	Signature
Date	Site

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Term	Explanation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	novel coronavirus 2019
CTCAE	Common Terminology Criteria for Adverse Events
DHEA	dehydroepiandrosterone
DTP	direct-to-patient
DXA	dual-energy x-ray absorptiometry
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDiary	electronic diary
EHP	Endometriosis Health Profile
EQ-5D-5L	European Quality of Life Five-Dimension Five-Level Scale
EU	European Union
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice
GnRH	gonadotropin-releasing hormone
HR	heart rate
ICH	International Council on Harmonisation
ID	identification
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NMPP	nonmenstrual pelvic pain
NRS	Numerical Rating Scale
NSAID	non-steroidal anti-inflammatory drug
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PLD	phospholipidosis

Term	Explanation
QTc	corrected QT (interval)
QTcF	QT interval by the Fridericia correction
SAP	statistical analysis plan
sB&B	Subject Modified Biberoglu and Behrman
SDV	source data verification
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
ULN	upper limit of normal
US	United States
W	Week
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. PROTOCOL SYNOPSIS

Study Title	SPIRIT EXTENSION: An International Phase 3 Open-Label, Single-Arm, Safety and Efficacy Extension Study to Evaluate Relugolix Co-Administered with Low-Dose Estradiol and Norethindrone Acetate in Women with Endometriosis-Associated Pain
Protocol Number	MVT-601-3103
Location	Multinational, including North and South America, Europe, Africa, New Zealand, and Australia
Study Centers	Approximately 320 sites
Study Phase	Phase 3
Target Population	Women aged 18 to 51 years diagnosed with endometriosis-associated pain
Number of Patients Planned	Approximately 800
Study Objectives	In women with endometriosis-associated pain, the study objectives are as follows: <u>Primary Efficacy Objectives</u> To be assessed at Week 52 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. To be assessed at Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.
	<u>Secondary Efficacy Objectives</u> To be assessed at Week 52 and Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: o Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; o Dysmenorrhea, as measured by the Numerical Rating Scale (NRS) for dysmenorrhea; o Patient Global Impression of Change (PGIC) for dysmenorrhea; o Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; o Overall pelvic pain, as measured by the NRS; o Analgesic use;

	○ PGIC for NMPP; ○ Dyspareunia, as measured by the NRS; ○ PGIC for dyspareunia; ○ Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]); ○ 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 EHP-30 Pain Domain; ○ Patient Global Assessment (PGA) for pain; ○ PGA for function; ○ Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains; ○ Dysmenorrhea-related functional effects (sB&B); ○ NMPP-related functional effects (sB&B).
	Safety Objectives • To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including: ○ Adverse events; ○ Changes in bone mineral density. Pharmacodynamic Objective • To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.
	Exploratory Objective • To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).
Study Design The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive open-label oral relugolix 40 mg once daily co-administered with low-dose- estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment	

during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 80 weeks. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via dual-energy x-ray absorptiometry (DXA).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, mammograms (for patients required to have this procedure; see Section 6.5.2.9), endometrial biopsies, and bone mineral density with DXA.

Determination of bone mineral density by DXA at the Early Termination or Week 104 visit and follow-up of findings will proceed according to the following rules:

Early Termination and 6-Month Post-Treatment DXA

- For patients who Early Terminate:
  - For Early Termination occurring **before Week 36**, DXA is not required at the Early Termination visit unless it will aid in the assessment of an adverse event or if the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2%

relative to the parent study baseline. In this case, follow-up DXA is required at 6 months (± 1 month).

- For Early Termination occurring **at or after the Week 36 visit**, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.
  - Most recent DXA was at the Week 24 visit: Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline.
  - Most recent DXA was after the Week 24 visit: Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.

Study Completion and 6-Month Post-Treatment DXA

- For patients who complete the open-label extension study:
  - Follow-up DXA is required at 6 months (± 1 month) if, at the Week 104 visit or on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.

  Note: Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.

12-Month Post-Treatment DXA

- If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with the parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study drug. If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with the parent study baseline, patients are recommended to be referred to and strongly encouraged to see a bone specialist for further evaluation of the bone loss.

  Note: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan once the consultation is complete.

Status of menstruation recovery will be documented at the Follow-Up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient. A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study (see Section 6.5.2.9).

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-Up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 months (± 1 month) and status of menstruation recovery, may be waived.

Inclusion/Exclusion Criteria

Inclusion Criteria: A woman will be eligible for enrollment in this study only if all of the following inclusion criteria apply and have been met at the time of the Week 24/Baseline visit:

1. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.
3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable non-hormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified non-hormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria: None of the following criteria may be true for a patient to be eligible for enrollment into this study.

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;

5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;
6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or
    b. The presenting visual acuity score has decreased by ten or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.
12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor;
13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).

Dose and Route of Administration	Test Product (all patients) • Relugolix 40 mg tablet will be co-administered orally once daily with 1.0 mg estradiol/0.5 mg norethindrone acetate. The low-dose hormonal add-back therapy will be over-encapsulated. Study treatment will be administered on an empty stomach.

Duration of Treatment	Study treatment will be self-administered for 80 weeks (Open-Label Treatment Period). Concomitant Medicinal Products Systematically Prescribed for All Study Patients Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug and a second-line opioid or opioid/acetaminophen or opioid/paracetamol combination for endometriosis-related pain relief as required. The specific analgesic drugs offered may differ for different countries or regions. The analgesics for each patient will be the same as those prescribed for her during the parent study.
Criteria for Evaluation	Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and Week 52, and between the parent study Baseline and the end of the extension study (Week 104) for the following parent study treatment groups: • Parent Study Group A: Randomized to 24 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group B: Randomized to 12 weeks of oral relugolix 40 mg once daily followed by 12 weeks of oral relugolix 40 mg once daily co-administered with 1.0 mg estradiol and 0.5 mg norethindrone acetate in the parent study; • Parent Study Group C: Randomized to placebo in the parent study. The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study. Primary Efficacy Endpoints Week 52 • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. Week 104 • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores.
	Secondary Efficacy Endpoints To be assessed at Week 52 and Week 104, unless otherwise specified • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea (at Week 52 only);

	• Change from the parent study Baseline in the mean NMPP NRS score; • Change from the parent Baseline in the mean NRS score; • Proportion of patients not using opioids; • Proportion of patients not using analgesics; • Proportion of patients who are better or much better on the PGIC for NMPP (at Week 52 only); • Change from the parent study Baseline in the mean dyspareunia NRS scores; • Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only); • Change from the parent study Baseline in the mean dyspareunia functional impairment on the sB&B scale; • Change from the parent study Baseline in severity scores on the PGA for pain; • Proportion of responders based on their EHP-30 Pain Domain score; • Change from the parent study Baseline in function impairment on the PGA for function; • Change from the parent study Baseline in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image); • Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B); • Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).
	<u>Safety Endpoints</u> To be assessed at Week 52 and Week 104 • Incidence of adverse events; • Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by DXA. <u>Pharmacodynamic Endpoint</u> To be assessed at Week 52 and Week 104 • Change from parent study Baseline in predose concentrations of serum estradiol. <u>Exploratory Endpoints</u> To be assessed at Week 52 and Week 104 • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.
Statistical Methods Efficacy and safety data will be analyzed using descriptive statistics by the originally randomized treatment groups. There will be no between-treatment group comparisons for the extension study data. There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.	

Efficacy

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

The point estimate and 2-sided 95% confidence interval (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

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

Safety

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA scan, mammograms (for patients required to have this procedure, see Section 6.5.2.9), and endometrial biopsy. Safety data analyses will use data from all patients from the parent studies who receive any amount of study drug (ie, from parent study Baseline to Week 52 or Week 104).

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, high level term, and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug, and severity. Laboratory values will be classified by toxicity grade based on the National Cancer Institute CTCAE. Laboratory shift tables of the parent study Baseline results to each of the subsequent visits will be produced.

Bone mineral density will be evaluated in all patients at the lumbar spine (L1-L4), femoral neck, and total hip at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits. The absolute change and percent change from parent study Baseline and Z-scores will be summarized by visit and parent study treatment group.

The mean percentage change from parent study Baseline to Week 52 in bone mineral density and corresponding 95% CI will be provided for each treatment group. For patients who were randomized to 24 weeks of treatment with relugolix and add-back in the parent studies (Group A in MVT-601-3101 or MVT-601-3102) and enrolled in the extension study, the lower bound of the 95% CI for mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, bone mineral density loss for the relugolix add-back treatment will be considered insignificant. The 95% CI for mean percentage change at Week 104/Early Termination from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104/Early Termination as supportive analyses.

Sample Size Estimation

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study (MVT-601-3101 or MVT-601-3102) and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

1.1. Schedule of Activities

Table 1-1 Schedule of Activities for Study MVT-601-3103

	PERIOD										SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Informed Consent	X[c]											
Review Eligibility Criteria	X											
Concomitant Medications[d]	X[e]	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (BP, HR, Temperature)	X[f]	X	X	X	X	X	X	X	X	X	X[g]	X
Weight	X[g]		X			X		X		X	X[h]	
Complete Physical Examination	X[g]					X[h]				X[i]	X[h]	
Visual Acuity[j]	X[g]											
Signs and Symptoms-Directed Physical Examination[k]		X	X	X	X		X	X	X		X[h]	X
12-Lead ECG[l]	X[g]					X				X[h]	X[h]	
Clinical Laboratory Tests[m]	X[g,n]	X	X	X	X	X[n]	X	X	X	X[n]	X[h]	X[ee]
Pharmacodynamics Sample[o]	X[g,n]					X[n]				X[n]	X[h,n]	

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Urinalysis	X[g]					X				X	X[h]	
Pregnancy Test (Urine)	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Daily eDiary[p]	X[g]	X	X	X	X	X	X	X	X	X		X
Site Review of eDiary Data	X[g]	X	X	X	X	X	X	X	X	X	X[h]	X
Bone Densitometry[q]	X[g]		X			X[r,s]				X[r,s]	X[h]	X[ee]
Endometrial Biopsy	X[g,t]					X				X[t]	X[h]	X[ee]
Dispense Study Treatment	X	X	X	X	X	X	X	X	X		X[h]	
Dispense or Prescribe Protocol-Specified Analgesic Drugs[u]	X	X	X	X	X	X	X	X	X		X[h]	
Treatment Compliance		X	X	X	X	X	X	X	X	X	X[h]	
Take Study Drug Dose in Clinic	X[v]					X				X	X[h]	
Daily Self-Administration of Study Treatment[w]		X ---------- X										
Take Protocol-Specified Rescue Analgesics as Needed[x]		X ---------- X										
EHP-30 Questionnaire[y]	X[g]		X		X	X		X		X	X[h]	

	PERIOD											SAFETY FOLLOW-UP
VISIT NAME (Timing is relative to MVT-601-3101/-3102)	**Week 24/Baseline (Week 24 of Parent Study; Baseline of Extension Study)**	**Week 28 and Week 32**	**Week 36**	**Week 40 and Week44**	**Week 48**	**Week 52[a]**	**Week 65**	**Week 78**	**Week 91**	**Week 104[a]/ Early Termination**	**Un-scheduled[b]**	**Follow-Up[c] (~30 days after last dose of study drug)**
Visit Window (days)	**Parent Study Day 169 -10/+20**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**-**	**-3 to +18**
Patient Global Assessment for Pain[y]	X[g]	X	X	X	X	X	X	X	X	X	X[h]	
[on paper] Patient Global Assessment for Function[z]	X[g]	X	X	X	X	X	X	X	X	X	X[h]	
Patient Global Impression of Change[y]	X[g]		X			X					X[h]	
[on paper] EHP Work Domain[z]	X[g]					X		X		X	X[h]	
EQ-5D-5L Questionnaire[y]	X[g]					X		X		X	X[h]	
Adverse Event Collection[aa]	X	X	X	X	X	X	X	X	X	X	X	X
Status of Menstruation Recovery												X[bb,ee]
Telephone Contact[cc]						X (W57)	X (W71)	X (W85)	X (W98)			
Mammogram[dd]						X[dd]				X[dd]	X[dd]	

BP = blood pressure; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; eDiary = electronic diary; EHP = Endometriosis Health Profile; EQ-5D-5L = European Quality of Life Five-Dimension Five-Level Scale; HR = heart rate; NRS = Numerical Rating Scale; PGA = Patient Global Assessment; sB&B = Subject Modified Biberoglu and Behrman; W = week.

[a] The Week 52 visit should occur on or after the 1-year anniversary of Baseline Day 1 of the parent study (± 7 days), and the Week 104 visit should occur on or after the 2-year anniversary of Baseline Day 1 of the parent study.

[b] Unscheduled visits may be conducted at the investigator's discretion when needed. The reason for the visit will be captured in the source documents.

[c] The Follow-up visit may be waived if the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit.

[d] May be signed up to 30 days prior to the Week 24/Baseline visit or during the Week 24/Baseline visit. Enrollment in MVT-601-3103 is defined by administration of the first dose of MVT-601-3103 study drug.

[e] Record all prescription and nonprescription drug and supplements taken from the Week 24/Baseline visit through the Safety Follow-Up Period. Concomitant medications with start date prior to the first dose of study drug for MVT-601-3103 should be reported as concomitant medications in the parent study (MVT-601-3101 or MVT-601-3102). If concomitant medication is ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.

[f] Concomitant medications are recorded both for the parent study and for MVT-601-3103 at the Week 24/Baseline visit. (See footnote e for further details).

[g] This is a parent study (MVT-601-3101 or MVT-601-3102) Week 24 procedure that serves as the Week 24/Baseline procedure for MVT-601-3103 and is covered under the informed consent for the parent study.

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

[i] The Week 52 and Week 104 physical examinations will include a breast examination.

[j] See parent study protocols (MVT-601-3101 or MVT-601-3102) for instructions on testing visual acuity.

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

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

[m] Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, Week 91, and Week 104/Early Termination. At the Week 24/Baseline visit, Week 52 visit, and Week 104/Early Termination visit, additional tests will include the following: fasting (at least 8 hours) glucose, lipid profile, and hemoglobin A1c.

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

[o] For Week 24/Baseline samples, see the parent protocol (MVT-601-3101 or MVT-601-3102). At Week 104/Early Termination, collect a sample for analysis of estradiol concentrations only. On days when pharmacodynamics samples are collected, administer the study treatment after the pharmacodynamics sample collections are collected.

[p] All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study. 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 until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.

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

[r] See Section 6.5.2.6 for details on the timing and follow-up of bone densitometry.

[s] Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed based on the timing of the Early Termination visit. See Section 6.5.2.6.

[t] Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details) and at Week 52 and Early Termination visit for all patients. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension; however, patients will have the option to opt out.

[u] Please see Appendix 1 for list of protocol-specified analgesics and see the Investigator Site File for information on where and how to obtain protocol-specified analgesic medications by country. At the Week 104 visit, patients who will not be proceeding to another 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 another extension study, refer to the protocol for that next study.

[v] Pregnancy test must be negative before the study drug dose is administered. For patients whose Baseline Day 1 visit is conducted on a different day than the parent study Week 24 visit, perform an unscheduled pregnancy test at Baseline Day 1 prior to administering the first dose of study drug.

[w] Patients will take the first dose of the study drug for this study once daily starting with the Week 24/Baseline visit (taken at the visit). If necessary, for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.). The first dose of study drug for this extension study must not be taken until all parent study Week 24 procedures such as laboratory tests have been completed. Therefore, results of testing required for eligibility (eg, DXA) must be available on or prior to the Week 24/Baseline visit. The last dose of study drug will be taken in the clinic during the Week 104/Early Termination visit.

[x] Patients may only take their study-specified analgesics for pain. Analgesics should not be taken prophylactically (ie, in anticipation of pain).

[y] The patient will enter her response(s) into an electronic 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.

[z] The patient will enter her response onto a paper questionnaire at the site. Paper questionnaires should be done in the following order: PGA for function, EHP Work Domain.

[aa] Collect adverse events from the time that the first dose of study drug for MVT-601-3103 is administered. Adverse events with onset prior to the first dose of study drug for MVT-601-3103 should be reported as an adverse event in the parent study (MVT-601-3101 or MVT-601-3102). If events originating in the parent study are ongoing at the time of the first dose of study drug for MVT-601-3103, please see the Case Report Form Completion Guidelines for instructions for recording the follow-up status.

[bb] Patients whose menses have not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

[cc] A telephone call will be performed at Weeks 57, 71, 85, and 98. The following activities should be completed: a concomitant medication review, evaluation of adverse events, a reminder of compliance with non-hormonal contraception requirements and the need to call the investigator if pregnancy is suspected, and a review of eDiary and study medication compliance.

[dd] For patients ≥ 40 years old at the time of the Week 52 visit, Week 104 visit, or Early Termination visit only. See Section 6.5.2.9.

[ee] See Section 6.5.2.6, Section 6.5.2.7, and Section 6.5.2.8 to determine if additional follow-up is required.

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 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-oophorectomy 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

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

2.2.1. Indication

Relugolix co-administered with low-dose estradiol and norethindrone acetate is being developed as a once-daily oral medication for the treatment of 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 was discovered and initially studied by Takeda Pharmaceutical Company, Limited, before development rights outside of Japan and certain East Asian countries were licensed to Myovant Sciences GmbH.

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

3. STUDY OBJECTIVES AND ENDPOINTS

Descriptive assessments of long-term efficacy and safety will be made between the parent study Baseline and Week 52, and between the parent study Baseline the end of the extension study (Week 104) for the following parent study treatment groups:

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

The parent study Baseline will be used as the reference point for this extension study for all change from baseline-related endpoints. The pain scores during the Baseline Pain Assessment Period of the parent study will establish the patient's baseline for both the parent study and the extension study.

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

Objectives	Endpoints
Primary Efficacy	
To be assessed at Week 52 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 52 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain. To be assessed at Week 104 • To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on endometriosis-associated pain.	To be assessed at Week 52 • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their dysmenorrhea Numerical Rating Scale (NRS) scores; • Proportion of women who respond or maintain response at Week 52/Early Termination, based on their NMPP NRS scores. To be assessed at Week 104 • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their dysmenorrhea NRS scores; • Proportion of women who respond or maintain response at Week 104/Early Termination, based on their NMPP NRS scores.
Secondary Efficacy	
To be assessed at Week 52 and Week 104 To evaluate long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on the following: • Function, as measured by the Endometriosis Health Profile (EHP)-30 Pain Domain; • Dysmenorrhea, as measured by the NRS for dysmenorrhea; • Patient Global Impression of Change (PGIC) for dysmenorrhea; • NMPP, as measured by the NRS for NMPP; • Overall pelvic pain, as measured by the NRS;	To be assessed at Week 52 and Week 104, unless otherwise specified • Change from the parent study Baseline in the EHP-30 Pain Domain scores; • Change from the parent study Baseline in the mean dysmenorrhea NRS score; • Proportion of patients who are better or much better on the PGIC for dysmenorrhea (at Week 52 only); • Change from the parent study Baseline in the mean NMPP NRS score; • Change from the parent Baseline in the mean NRS score;

Objectives	Endpoints
• Analgesic use;	• Proportion of patients not using opioids; • Proportion of patients not using analgesics;
• PGIC for NMPP;	• Proportion of patients who are better or much better on the PGIC for NMPP (at Week 52 only);
• Dyspareunia, as measured by the NRS;	• Change from the parent study Baseline in the mean dyspareunia NRS scores;
• PGIC for dyspareunia;	• Proportion of patients who are better or much better on the PGIC for dyspareunia (at Week 52 only);
• Dyspareunia-related functional effects (Subject Modified Biberoglu and Behrman [sB&B]);	• Change from the parent study Baseline 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 function measured by the EHP-30 Pain Domain;	• Proportion of responders based on EHP-30 Pain Domain scores;
• Patient Global Assessment (PGA) for pain;	• Change from the parent study Baseline in severity scores on the PGA for pain;
• PGA for function;	• Change from the parent study Baseline in function impairment on the PGA for function;
• Endometriosis-associated quality of life, as measured by the EHP-30 Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image domains;	• Change from the parent study in each of the non-pain EHP-30 domains (Control and Powerlessness, Social Support, Emotional Well-Being, and Self-Image);
• Dysmenorrhea-related functional effects (sB&B);	• Change from the parent study Baseline pain assessment period in dysmenorrhea-related functional effects (sB&B);
• NMPP-related functional effects (sB&B).	• Change from the parent study Baseline pain assessment period in NMPP-related functional effects (sB&B).
Safety	
To evaluate the safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including:	To be assessed at Week 52 and Week 104
• Adverse events;	• Incidence of adverse events;

Objectives	Endpoints
• Changes in bone mineral density.	• Percent change from the parent study Baseline in bone mineral density at the lumbar spine (L1-L4), femoral neck, and total hip as assessed by dual-energy x-ray absorptiometry (DXA).
Pharmacodynamic	
• To evaluate the pharmacodynamic effects of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), on estradiol.	To be assessed at Week 52 and Week 104 • Change from parent study Baseline in predose concentrations of serum estradiol.
Exploratory	
• To evaluate the benefit of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate on endometriosis-associated quality of life (EHP-30 total score), work (EHP Work Domain), and patient-reported quality of life outcomes (European Quality of Life Five-Dimension Five-Level Scale [EQ-5D-5L]) for up to 104 weeks among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102).	To be assessed at Week 52 and Week 104 • Change from Baseline in the EHP-30 scale total score; • Change from Baseline in the EHP Work Domain score; • Change from parent study Baseline in the EQ-5D-5L.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design

The SPIRIT EXTENSION study is an international phase 3 open-label, single-arm, long-term efficacy and safety study that will enroll eligible patients who have completed their participation in one of the phase 3 randomized, double-blind, placebo-controlled parent studies (MVT-601-3101 or MVT-601-3102). All patients will receive open-label oral relugolix 40 mg once daily co-administered with low-dose estradiol 1.0 mg and norethindrone acetate 0.5 mg for up to 80 weeks. Approximately 800 women with endometriosis-associated pain will be enrolled. The objectives of the study are to evaluate long-term efficacy and safety through up to 104 weeks of treatment (including treatment during the parent study) of relugolix co-administered with low-dose estradiol/norethindrone acetate. Eligible patients will have completed participation in one of the parent studies and consented to participate in this extension study. Baseline procedures will be done at the same visit for this extension study (referred to as the "Week 24/Baseline visit" in this study) that coincides with the Week 24 visit from the parent study and will be defined as the date of completion of the last Week 24 procedure in the parent study. The Week 24/Baseline visit will include vital signs, physical examination, laboratory assessments, a 12-lead electrocardiogram (ECG), bone densitometry, patient-reported outcome assessments, and endometrial biopsy (if required). When Week 24 procedures in the parent study have been completed, the investigator will assess patient eligibility for participation in the open-label extension study. The eligibility assessment will be based on data available at the Week 24/Baseline visit. No MVT-601-3103 study procedures will be performed until the consent form for this extension study is signed.

Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. The administration of the first dose of study drug for MVT-601-3103 will define enrollment into this study. Study participants will then take the open-label study treatment (relugolix 40 mg co-administered with estradiol 1.0 mg and norethindrone acetate 0.5 mg) orally once daily for 80 weeks. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and with sponsor/designee approval, the first dose of open-label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, electronic diary [eDiary] completion, etc.).

During the 80-week Open-Label Treatment Period and the ~30-day Follow-Up Period, patients will continue to record study treatment, assessment of pain using the NRS, menstrual bleeding, analgesic use, and the functional effects of endometriosis-associated pain (sB&B) in the eDiary. Only study-specific rescue analgesic medications should be used starting with the Week 24/Baseline visit and through the Follow-Up visit and these medications will be taken for control of pain and not prophylactically. Health-related quality of life questionnaires; PGIC for dysmenorrhea, NMPP, and dyspareunia; and PGA for pain and function will be completed

during the visits on an electronic tablet or on paper, according to the Schedule of Activities (Section 1.1).

Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, mammograms (for patients required to have this procedure; see Section 6.5.2.9), endometrial biopsies, and bone mineral density with DXA.

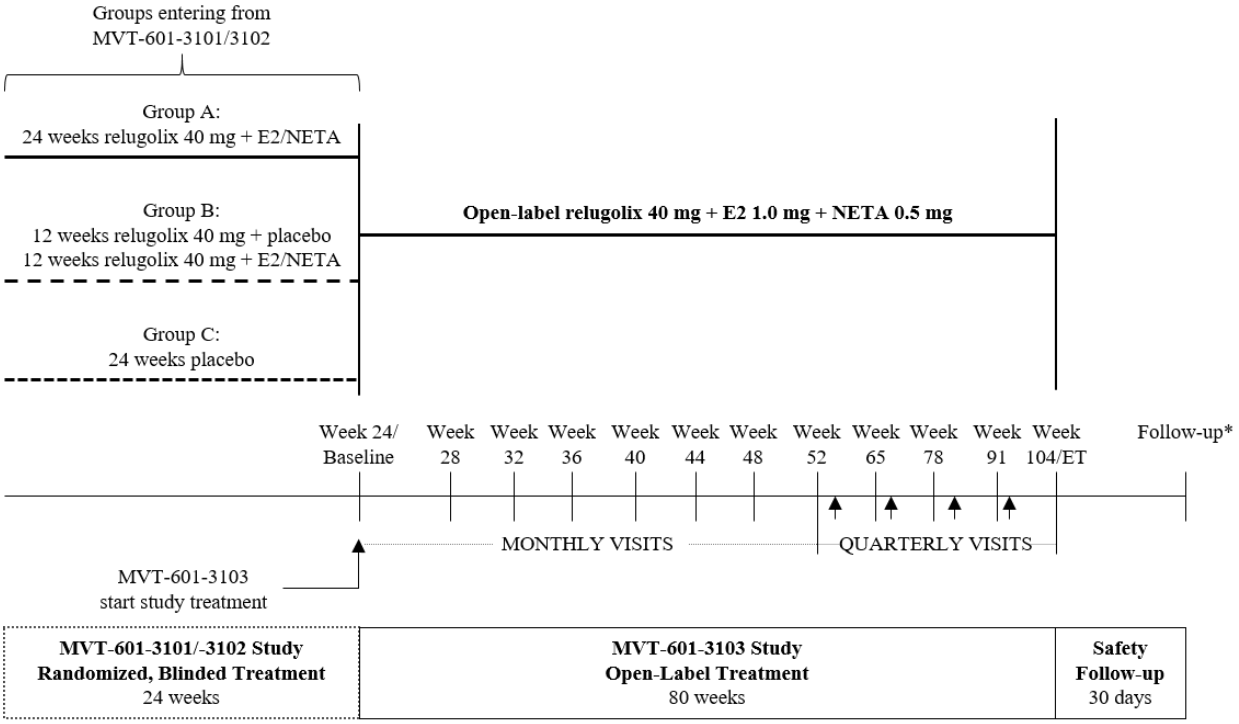
At the Week 36, Week 52, and Week 104/Early Termination visits, each patient will have an assessment of bone mineral density via DXA. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.

Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient. A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study (see Section 6.5.2.9).

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, then the Follow-Up visit and the follow-up procedures performed under this protocol, including the follow-up bone densitometry scan at 6 months (± 1 month) and status of menstruation recover, may be waived.

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

Figure 4-1 MVT-601-3103 Study Schematic



E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg; eDiary = electronic diary; ET = Early Termination.
* The Follow-up visit is schedule approximately 30 days after the last dose of study drug.
↑ Indicates telephone contact to review concomitant medication, evaluation of adverse events, and a review of eDiary and study medication compliance. To be conducted at Week 57, Week 71, Week 85, and Week 98.

4.2. Discussion of Study Design, Including Dosing

The SPIRIT EXTENSION study (MVT-601-3103) is an extension of 2 replicate, 24-week phase 3 studies (MVT-601-3101 and MVT-601-3102) designed to establish the efficacy and safety of relugolix 40 mg once daily in women with endometriosis-associated pain. This 80-week extension study provides additional efficacy and safety data up to 104 weeks to demonstrate the benefit and safety of relugolix co-administered with low-dose estradiol (1 mg) and norethindrone acetate (0.5 mg). The primary objectives of the study are to assess long-term efficacy of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks on dysmenorrhea and NMPP, common and burdensome symptoms of endometriosis. The study will also evaluate safety of relugolix 40 mg once daily co-administered with low-dose estradiol and norethindrone acetate for up to 104 weeks, among patients who previously completed a 24-week treatment period in one of the parent studies (MVT-601-3101 or MVT-601-3102), including adverse events and change in bone mineral density.

The dose of relugolix for phase 3 evaluation is 40 mg once daily. Data from a phase 2 study in women with endometriosis demonstrated relugolix 40 mg once daily suppressed estradiol levels to below 20 pg/mL in the majority of women, and results were similar to those in the group of women treated with leuprolide subcutaneous injection, 3.75 mg. Women in both the relugolix 40 mg and the leuprolide groups had similar reductions in pelvic pain, the primary endpoint of

the study. Finally, a phase 2 study of doses of relugolix 10, 20, or 40 mg once daily administered to women with heavy menstrual bleeding associated with uterine fibroids demonstrated the 40-mg dose provided the most reduction in menstrual blood loss and was the optimal dose to move forward into phase 3 development based on efficacy data.

However, data on bone mineral density from DXA scanning in both phase 2 studies of premenopausal women with endometriosis or uterine fibroids demonstrated relugolix 40 mg once daily resulted in a degree of bone mineral density loss that is only acceptable for short-term dosing. To mitigate this known adverse consequence of estrogen suppression, relugolix will be co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate in this phase 3 clinical study. This low-dose hormonal therapy is currently approved for long-term use to prevent bone mineral density loss and vasomotor symptoms in postmenopausal women. Although relugolix doses of 20 mg and 10 mg once daily had less bone mineral density loss, these doses did not provide adequate relief from endometriosis-associated pain to move forward into phase 3 clinical development and, based on the DXA data from the phase 2 study, are not expected to prevent bone mineral density loss in a significant majority of women over 104 weeks of treatment.

The co-administration of hormonal add-back therapy to relugolix aims to restore estradiol concentrations to a range that alleviates the adverse impact of the hypoestrogenic state on bone mineral density through 104 weeks of treatment, as well as on vasomotor symptoms such as hot flushes, but without substantial effect on the beneficial decrease in dysmenorrhea and NMPP. It is well known that bone is exquisitely sensitive to estrogen and low-doses of estrogen are sufficient to prevent bone mineral density loss in a hypoestrogenic state [Barbieri, 1992]. The combination of estradiol with a progestin is commonly used for long-term hormonal add-back therapy to reduce the risk of developing endometrial hyperplasia, which can occur with unopposed estrogen therapy [Activella US Prescribing Information, 2013]. A variety of add-back hormonal therapies have been evaluated in combination with GnRH agonists and antagonists over the last 20 years [Archer, 2015; Chwalisz, 2012; Franke, 2000; Hornstein, 1998; Morris, 2008; Simpson, 2015; Wu, 2014; Zupi, 2004], and a combination of estradiol and norethindrone acetate has been used as add-back therapy in prior clinical studies with leuprolide (a GnRH agonist) and more recently, the GnRH antagonist elagolix, in each case reducing bone mineral density loss and the incidence of hot flushes without a significant impact on the decrease in menstrual blood loss [Archer, 2017; Lee, 2016; Franke, 2000] or endometriosis-associated pain [Wu, 2014]. The estradiol/norethindrone acetate combination proposed for evaluation in this phase 3 study is currently approved in the United States (US) as long-term hormone replacement therapy to prevent bone loss and alleviate vasomotor symptoms in postmenopausal women [Activella US Prescribing Information, 2013].

A 6-week study in healthy premenopausal women administered oral relugolix 40 mg once daily alone or relugolix 40 mg once daily in combination with 1 mg estradiol and 0.5 mg norethindrone acetate demonstrated that this dose of add-back therapy maintains serum estradiol in the 25 to 50 pg/mL range, the range historically shown to reduce loss of bone mineral density [Barbieri, 1992]. Serum N- and C-telopeptide concentrations were also maintained at near baseline levels with the addition of the add-back therapy, suggesting reduced bone resorption compared to the group receiving relugolix alone. Hot flush rate was also considerably reduced with the addition of add-back therapy. The estrogenic metabolite of norethindrone acetate, ethinyl estradiol, was below the limit of quantitation in almost all pharmacokinetic samples collected, and therefore, will not be assessed in this phase 3 study. These data also confirm that

lower doses of estradiol/norethindrone acetate (such as the 0.5 mg/0.1 mg combination tablet [Activella US Prescribing Information, 2013]) would not provide sufficient serum estradiol concentrations to protect against the loss of bone mineral density resulting from the hypoestrogenic state induced by once daily administration of relugolix 40 mg.

The doses of estradiol and norethindrone acetate used in this study (1.0 mg and 0.5 mg, respectively) were used in the parent studies (MVT-601-3101 and MVT-601-3102) and represent less than one fifth the estrogenic effects of an oral contraceptive pill containing 30 µg of ethinyl estradiol. Therefore, this low-dose hormonal add-back therapy is added solely to improve the safety of relugolix therapy, and it is expected to have either a neutral or a marginal detrimental effect on efficacy, while mitigating the side effects of relugolix on bone mineral density loss and vasomotor symptoms.

In summary, relugolix at a dose of 40 mg once daily resulted in a significant decrease in endometriosis-associated pain in a well-designed large phase 2 study. However, its administration was associated with a degree of bone mineral density loss unacceptable for long-term treatment. This phase 3 study extension study will assess long-term efficacy and safety of relugolix 40 mg co-administered with low-dose estradiol and norethindrone acetate to decrease dysmenorrhea and NMPP and to prevent the bone mineral density loss and ameliorate some of the other side effects of a hypoestrogenic state such as hot flushes.

This open-label extension study will allow for a description of long-term efficacy data and safety for an additional 80 weeks of treatment, providing approximately 1 year of efficacy and safety data from the women originally randomized to relugolix in studies (MVT-601-3101 and MVT-601-3102). This study design will allow eligible patients with endometriosis-associated pain, including those randomized to placebo in the parent study, to receive relugolix co-administered with low-dose hormonal add-back therapy during the extension.

4.3. Selection of Study Population

The study population will include approximately 800 premenopausal women aged 18 to 51 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. Completed 24 weeks of study drug treatment and study participation in either MVT-601-3101 or MVT-601-3102;
2. Has voluntarily signed and dated the informed consent form prior to initiation of any study-specific procedures for MVT-601-3103;

   Note: Procedures conducted as part of the parent study that also serve as baseline procedures for this study will be done under the informed consent for the parent study.

3. 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;
4. Has a negative urine pregnancy test at the Week 24/Baseline visit;
5. Has agreed to continue to use only study-specified analgesic medications during the study and is not known to be intolerant to these;
6. Agrees to continue to use acceptable non-hormonal contraceptive methods as described in Section 4.6 consistently during the Open-Label Treatment Period and for at least 30 days after the last dose of study drug. However, the patient is not required to use the specified non-hormonal contraceptive methods if she:
   a. Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
   b. Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure™), at least 6 months prior to the Week 24/Baseline visit (patients with Essure must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;
   c. Has a non-hormonal intrauterine device (eg, Paragard®) placed in the uterus;
   d. Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as noted above;
   e. Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

Exclusion Criteria

1. Has had a surgical procedure for treatment of endometriosis at any time during the parent study (MVT-601-3101 or MVT-601-3102);
2. 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;
3. 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);
4. Has a Z-score < -2.0 or has a ≥ 7% decrease in bone mineral density from the parent study Baseline at lumbar spine, total hip, or femoral neck based on the parent study Week 24 DXA assessment of bone mineral density;
5. Anticipated to use any prohibited medications as detailed in Section 5.10.1;

6. Has any contraindication to treatment with low-dose estradiol and norethindrone acetate, including:
   a. Known, suspected, or history of breast cancer;
   b. Known or suspected estrogen-dependent neoplasia;
   c. Active deep vein thrombosis or pulmonary embolism, or history of these conditions prior to the Week 24/Baseline visit;
   d. History of or active arterial thromboembolic disease, including stroke and myocardial infarction;
   e. Known anaphylactic reaction or angioedema or hypersensitivity to estradiol or norethindrone acetate;
   f. Known protein C, protein S, or antithrombin deficiency, or other known thrombophilia disorders, including Factor V Leiden;
   g. Migraine with aura;
   h. History of porphyria;
7. Has current active liver disease from any cause;
8. 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;
9. Had any of the following clinical laboratory abnormalities at the parent study Week 20 visit or, if available, any subsequent visit in one of the parent studies (MVT-601-3101 or MVT-601-3102):
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.0 times the upper limit of normal (ULN); or
   b. Bilirubin (total bilirubin) > 1.5 x ULN (or > 2.0 x ULN if secondary to Gilbert syndrome or pattern consistent with Gilbert syndrome);
10. Is currently pregnant or lactating, or intends to become pregnant during the study period or within 1 month after the last dose of study drug, or plans to donate ova during the study period or within 2 months after the last dose of study drug;
11. Has a decline in presenting visual acuity score, as defined below (unless explained by refractive error or approved by the sponsor):
    a. 90 or lower and 5 or more points lower at Week 24/Baseline visit relative to the parent study Baseline visit; or
    b. The presenting visual acuity score has decreased by ten or more points at the Week 24/Baseline visit relative to the parent study Baseline visit;

    Note: Visual acuity score must have been obtained with corrective lenses, if applicable.

12. Is inappropriate for participation in this study because of conditions that may interfere with interpretation of study results or prevent the patient from complying with study requirements, as determined by the investigator, sub-investigator, or medical monitor;
13. Met a withdrawal criterion in the parent study (MVT-601-3101 or MVT-601-3102).

4.4. Method of Assigning Patients to Treatment Group and Patient Identification Number

Eligible patients who sign consent will be identified with the same Patient Identification (ID) Number assigned to the patient during the parent study. This extension study is a single-arm, open-label study, and thus all eligible patients are assigned to the same treatment group of relugolix 40 mg co-administered with low-dose of estradiol and norethindrone acetate (see Section 5.1 for treatment details).

4.5. Removal of Patients from Therapy

Completion of the Week 104 visit defines completion of the study. Patients may withdraw consent to participate in the study and discontinue treatment at any time for any reason. Investigators or the medical monitor may remove patients from therapy under this protocol for reasons of safety and/or lack of compliance as discussed below. Patients removed from therapy for any reason will undergo the assessments for the Early Termination visit (see the Week 104 visit on the Schedule of Activities, Section 1.1) and will have a Follow-up visit to assess safety approximately 30 days after the end of study drug treatment (ie, after the patient's last dose of study medication). When patients complete the study or early terminate from the study, they must be deactivated from the study in the interactive voice response system/interactive web response system (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 enrollment that a patient failed to meet protocol entry criteria and continued participation poses an unacceptable risk to the patient's health;
- If the following liver test abnormalities develop, study drug should be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests, until a patient's laboratory profile has returned to normal/baseline status):
  - ALT or AST > 8 x ULN; or
  - ALT or AST > 5 x ULN and persists for more than 2 weeks; or
  - ALT or AST > 3 x ULN in conjunction with elevated total bilirubin > 2 x ULN or international normalized ratio (INR) > 1.5; or
  - ALT or AST > 3 x ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%);

- QT interval by the Fridericia correction (QTcF) prolongation of more than 500 msec read by a cardiologist;
- Evidence of endometrial hyperplasia or endometrial carcinoma on endometrial biopsy;
- If the patient has a ≥ 7% loss of bone mineral density at lumbar spine, total hip, or femoral neck compared with the parent study Baseline;
- If the patient, in the opinion of the investigator or the medical monitor, is grossly noncompliant with the protocol's requirements. Gross noncompliance includes < 75% compliance with the study drug over > 2 consecutive months; missing multiple study visits; and persistent (> 2 consecutive months) noncompliance (< 50% of the required number of days) with eDiary completion up to Week 52 or persistent (≥ 2 eDiary collection cycles) noncompliance (< 50% of the required number of days) with eDiary completion from Week 52 to Week 104. Investigators will follow up with the patient and encourage compliance with study drug or eDiary prior to discontinuing her from the study;
- If the patient becomes pregnant at any time after providing a signed informed consent form, the patient must be withdrawn immediately (see Section 7.8 for information on pregnancy reporting);
- Evidence of malignant breast lesion(s) or breast carcinoma on Week 52 or Week 104/Early Termination or most recent mammogram or additional breast imaging (see Section 6.5.2.9 for more information on mammogram at Week 52 or Week 104/Early Termination).

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

4.6. Contraception/Pregnancy Avoidance

All patients should be counseled at every visit to adhere to the use of protocol allowed contraceptive methods. In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study including through 30 days following the last dose of study drug, unless any of the following apply:

- Has a sexual partner(s) who was vasectomized at least 6 months prior to the Week 24/Baseline visit;
- Had a bilateral tubal occlusion (including ligation and blockage methods such as Essure) at least 6 months prior to the Week 24/Baseline visit (patients with Essure

must have prior confirmation of tubal occlusion by hysterosalpingogram) and there must be no evidence of post-Essure syndrome;

- Has a non-hormonal intrauterine device (eg, Paragard) placed in the uterus;
- Is not sexually active with men; periodic sexual relationship(s) with men requires the use of non-hormonal contraception as described below;
- Practices total abstinence from sexual intercourse, as her preferred lifestyle; periodic abstinence is not acceptable.

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

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

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

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

Urine pregnancy tests will be performed according to the Schedule of Activities (Table 1-1; including just prior to receiving the first dose of study drug), and patients will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures. Patients should call the investigator immediately if they suspect they may be pregnant. Patients who become pregnant during the study will be withdrawn from the study and followed for pregnancy outcome (see Section 7.8).

4.7. Novel Coronavirus 2019 Guidance

Guidance for conducting clinical trials during the novel coronavirus 2019 (COVID-19) pandemic is included in Appendix 9.

5. TREATMENTS

5.1. Treatments Administered

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

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

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

Table 5-1 Description of MVT-601-3103 Study Drugs

Name of Investigational Product	Relugolix	Estradiol / Norethindrone Acetate
Formulation Description	Round film-coated pink tablet	A Swedish orange, over-encapsulated round film-coated white tablet with back-fill material
Dosage Form	Tablet	Capsule
Unit Dose Strength	40 mg	Estradiol 1.0 mg / norethindrone acetate 0.5 mg
Route of Administration/ Duration	Oral once daily/ 80 weeks	Oral once daily/ 80 weeks

Two protocol-specified analgesics include a first-line non-steroidal anti-inflammatory drug (NSAID) and a second-line opioid or opioid/acetaminophen (or paracetamol) 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 1. 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 common excipients.

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

5.3. Randomization and Stratification

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

5.4. Directions for Administration

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

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

On Week 24/Baseline 1, Week 52, and Week 104 clinic visit days, study drug will be administered in the clinic rather than at home (see Schedule of Activities in Section 1.1).

5.5. Dose Reduction/Dose Administration

No toxicity-related dose reductions of study drug are permitted. Patients who experience a grade 3 or greater toxicity that cannot be ameliorated by the use of adequate medical intervention should have their treatment interrupted until the toxicity improves to a grade 2 or lower severity. 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. Study drug should be stored protected from light. A daily temperature log of the drug storage area must be maintained every working day. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. Only patients enrolled in the study may receive study drug, and only authorized site staff may supply or administer study drug. Further guidance and information for final disposition of unused study drug are provided in the Investigator Site File. 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 lot/batch 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 and the estradiol/norethindrone acetate combination to be distributed will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

Please see Appendix 1 for a list of protocol-specified analgesics. Further details on analgesic medication are provided in the Investigator Site File.

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. The study-specified pain medications for each patient will be the same as for the parent study. Only study-specific Tier 1 and Tier 2 analgesic medications (see Appendix 1) should be taken starting with the Baseline/Week 24 visit and subsequently. Analgesic medications will be taken for control of pain and not prophylactically.

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 when appropriate.

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 at the time of enrollment into this study. 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 the time of enrollment in this study, 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 eDiary.

5.8. Blinding

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

5.9. Study Drug Accountability and Treatment Compliance

Patients should complete their eDiary each day on study and should bring all unused and used (including partially used) study drug kits to each study visit. At the Week 24/Baseline visit and

Week 104/Early Termination visit, all used, partially used, and unused study drug kits should be retained at the site. At all other visits, only fully used study drug kits should be retained at the site. New study drug should be dispensed as described in Section 1.1 (Schedule of Activities).

Study drug accountability will be conducted and results will be recorded. If a patient is persistently noncompliant with the study treatment, it may be appropriate to withdraw the patient from the study (see Section 4.5). All patients should be reinstructed about the dosing requirement during study contacts. The authorized study personnel conducting the re-education must document the process in the patient's source records.

Because of the importance to both safety and efficacy evaluation, patients who are grossly noncompliant with eDiary completion must undergo an Unscheduled visit to evaluate reasons for noncompliance 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 4.5 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. Prior and Concomitant Medications and Non-Drug Therapies

5.10.1. Prohibited Medications

Table 5-2 provides examples of prohibited drug categories; however, it is not a comprehensive list of all restricted medications. Drugs and drug classes in Table 5-2 are prohibited at any time during the study through the Follow-Up visit, except as noted in the table. Consult the medical monitor if there is any uncertainty regarding patient use of a particular drug or drug class.

Table 5-2 Prohibited Medications

Drug Class	Examples	Comments
Bisphosphonates	alendronate etidronate zoledronic acid	
GnRH analogues	leuprolide acetate injection, also known as leuprorelin goserelin acetate injection	
Anti-androgens	danazol	
Anticonvulsant drugs (specified)	phenobarbital carbamazepine phenytoin valproic acid primidone	Note: All other anticonvulsants are allowed.
Aromatase inhibitors	anastrozole letrozole	

Drug Class	Examples	Comments
Progestins and progestin implants	dienogest norethindrone medroxyprogesterone cyproterone etonogestrel	
Estrogens	estradiol valerate conjugated estrogens ethynyl estradiol	
Hormonal contraceptives, contraceptive patches and vaginal rings	combined or progestin only NuvaRing	
Selective estrogen receptor modulators	raloxifene bazedoxifene lasofoxifene clomifene tamoxifen	
Selective progesterone receptor modulators	mifepristone ulipristal acetate	
Over-the-counter and herbal products/teas with known hormonal activity	plant-based estrogen products "natural" thyroid supplements dihyroepiandrosterone (DHEA)	
Intrauterine devices	levonorgestrel	
Bone agents	calcitonin calcitriol ipriflavone teriparatide denosumab abaloparatide odanacatib romosozumab	Calcium and Vitamin D2 and Vitamin D3 (ergocalciferol and cholecalciferol) are allowed without restriction.
Glucocorticoids	prednisolone or prednisone dexamethasone	Anticipated use of systemic glucocorticoids at an oral prednisone-equivalent dose of more than 5 mg every other day during the study. Note: topical, inhaled, intranasal, otic, ophthalmic, intraarticular, or intralesional subcutaneous are permitted without restriction. Short duration (< 21 days) higher-dose glucocorticoids required for acute events are permitted during the study.

Drug Class	Examples	Comments
P-glycoprotein inducers	avasimibe carbamazepine phenytoin rifampin St. John's wort tipranavir/ritonavir[f]	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.
Moderate and strong P-glycoprotein- inhibitors	amiodarone azithromycin[a] captopril[b] carvedilol clarithromycin[a] conivaptan cyclosporin[c] diltiazem dronedarone erythromycin[a] felodipine[d] itraconazole[e] ketoconazole[e] lopinavir/ritonavir[f] quercetin quinidine ranolazine ticagrelort[g] verapamil	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.
Analgesic drugs **other** than those specified for use during the study[h]	Acetaminophen/paracetamol (other than any included in a study-specified analgesic) aspirin > 325 mg/day NSAIDs (other than study-specified NSAIDs) gabapentin pregabalin carbamazepine metamizole cannabinoids	Note: Aspirin ≤ 325 mg per day is allowed.

Drug Class	Examples	Comments
Antidepressants New treatment or changed doses of SSRI, SNRI, or TCA antidepressants	**SNRI examples:** duloxetine venlafaxine desvenlafaxine **SSRI examples:** citalopram fluoxetine paroxetine fluvoxamine **TCA examples:** amitriptyline doxepin desipramine nortriptyline	SSRI, SNRI, or TCA allowed if given at the same dose as used during the 3 months prior to the Run-In Period of MVT-601-3101 or MVT-601-3102. 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.

DHEA = dihydroepiandrosterone; GnRH = gonadotropin-releasing hormone; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

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.
h. For situations where non-study analgesics may be allowed, see Section 5.7.

5.10.2. Permitted Medications

All concomitant medications used during the study will be recorded in the electronic Case Report Forms (eCRFs), including the drug generic name, dose amount, route of administration, start date, and stop date.

5.10.2.1. Analgesics

All analgesics will be collected in the eDiary and recorded in the eCRFs.

5.10.3. Prohibited Non-Drug Therapies

Surgical treatment of endometriosis is prohibited from the Week 24/Baseline visit until the patient's final study visit unless urgently needed for patient safety.

6. STUDY ASSESSMENTS AND PROCEDURES

The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File. Guidelines to address the COVID-19 pandemic are included in Appendix 9.

6.1. Schedule of Observations and Procedures

Assessments should be completed at the designated visit/time points as described in the Schedule of Activities (see Section 1.1). The study is divided into 2 periods: Open-Label Treatment Period and Safety Follow-Up Period. Unscheduled visits may occur as needed to evaluate patients.

6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)

As denoted in the Schedule of Activities (see Section 1.1), certain Week 24 visit procedures of MVT-601-3101 or MVT-601-3102 will serve as the Week 24/Baseline procedures for patients who are interested in participating in this extension study, and these Week 24 procedures will be performed under the informed consent for the parent study.

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

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

- Informed consent (unless signed previously);
- Record concomitant medications;
- Update the patient's status in the IVRS/IWRS as being in the MVT-601-3103 and receive the lot numbers for study drug allocation;
- Dispense study treatment;
- Dispense or prescribe protocol-specified analgesic drugs;
- Transition the patient within her eDiary from the parent study to MVT-601-3103;
- Take study drug dose in clinic; and
- Record adverse events, if any.

The Week 24 visit date in the parent study is defined as the date that the last procedures for the Week 24 visit were completed, acknowledging that the Week 24 visit procedures may be completed on different dates. Patients will have received their last dose of study drug in the parent study on the day prior to the Week 24/Baseline visit and will receive their first dose of study drug for this extension study in the clinic after the patient is determined to be eligible for this extension study and has provided informed consent to participate. Therefore, results of testing required for eligibility must be available on or prior to the Week 24/Baseline visit. If necessary for logistical reasons (eg, delayed availability of study drug supply on site, others), and

with sponsor/designee approval, the first dose of open label study drug for MVT-601-3103 may be administered up to 10 days following the parent study Week 24/Baseline visit. If the first dose of study drug is not given during this up to 10-day interval, the parent study follow-up procedures should be followed (ie, adverse event reporting, eDiary completion, etc.).

Patients will continue recording data in their eDiary daily and taking protocol-specified analgesics as needed until Week 52. After Week 52, the eDiary will be collected on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit. Following the Week 24/Baseline visit, on-treatment study visits will occur at Weeks 28, 32, 36, 40, 44, 48, 52, 65, 78, 91, and 104. Sites will monitor diary completion using the Trial Manager web portal throughout the study.

A telephone call will be performed at Weeks 57, 71, 85 and 98. The following activities should be completed: a concomitant medication review, an evaluation of adverse events, a review of study medication compliance, a reminder of compliance with non-hormonal contraception requirements and the need to call the investigator if pregnancy is suspected, and a reminder to the patient to start recording in the eDiary daily.

Accountability for study drug will be performed at each visit. Instructions for analgesic medication usage will be reinforced at each visit.

Questionnaires are administered on the electronic tablet and on paper at each visit. These procedures should occur before any other types of study procedures are performed. When both electronic tablet and paper questionnaires are required at a visit, 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 function
  - EHP Work Domain [Week24/Baseline, Week 52, Week 78, and Week 104 only]

Patients will bring their eDiary, analgesic medications, and study drug to each visit. The site must document the start and stop dates of the patient's menses.

An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details). An endometrial biopsy is required at Week 52 and the Early Termination visit for all patients. This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, Week 91, and Week 104/Early Termination. At the Week 24/Baseline

visit, Week 52 visit, and Week 104/Early Termination visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.

Electrocardiograms will be performed at the Week 24/Baseline, Week 52, and Week 104/Early Termination visits.

A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study (see Section 6.5.2.9).

Bone densitometry will occur at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits. Follow-up of bone densitometry findings will proceed according to the rules described in Section 6.5.2.6.

Bone densitometry and ECGs will be submitted for central reading.

Study drug compliance will be reviewed at each visit. Fasting (other than water) for at least 8 hours is required prior to blood sampling on Week 24/Baseline and Week 52/Early Termination visits and for 1 hour after administration of the study drug in the clinic. Laboratory requisitions must indicate whether or not the patient was not fasted for their chemistry and lipid testing.

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

6.3. Early Termination Visit and Follow-Up Visit

All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event. Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.

Patients (including those who complete the Week 104 visit and those who withdraw early from this study) will have a Follow-Up visit approximately 30 days after the last dose of study drug, or prior to the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention or other invasive procedure for endometriosis, whichever occurs first. However, for patients who enroll directly into another relugolix clinical study upon completion of the Week 104 visit, the Follow-Up visit may be waived.

The Follow-Up visit will be used to assess safety after discontinuation of study treatment including adverse events, clinical safety laboratories, and return of menstruation. Refer to the Schedule of Activities (see Section 1.1) for individual study visit procedures during the Follow-Up visit.

6.4. Unscheduled Visits

Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, mammogram (for patients required to have this procedure; see Section 6.5.2.9), 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc., may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.

6.5. Study Procedures

6.5.1. Efficacy-Related Procedures

6.5.1.1. Pharmacodynamics Sample Collection

A blood sample for the pharmacodynamic analysis of serum estradiol will be collected predose at the visits indicated in the study Schedule of Activities (see Section 1.1), other than at the Week 104 or the Early Termination visit, when no dose is administered. These pharmacodynamic samples will be analyzed at a central laboratory. These results will not be shared with the sites at any time.

6.5.1.2. Patient eDiary

All women enrolled in the study will continue to use the patient eDiary dispensed in the parent study (see Appendix 2). 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 until Week 52. After Week 52, eDiary scores will be entered over four eDiary collection cycles on the following schedule: Week 57 to the Week 65 visit, Week 71 to the Week 78 visit, Week 85 to the Week 91 visit, and Week 98 to the Week 104 visit.

The site should review the eDiary data at every visit.

6.5.1.3. 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 3). Patients will complete the EHP-30 questionnaire at the site at visits indicated in Section 1.1 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.

6.5.1.4. 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 4). 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 visits indicated in Section 1.1 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.

6.5.1.5. 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 5) 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. The PGA for pain severity and the PGIC will be completed on a tablet device at the study site. The PGA for function will be completed on a paper questionnaire at the study site.

6.5.1.6. 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 6). Patients will complete the EHP Work Domain questionnaire at visits indicated in Section 1.1 before other types of study procedures, such as blood draws and physical examinations, are performed. The EHP Work Domain will be completed on a paper questionnaire at the study site.

6.5.2. Safety-Related Procedures

6.5.2.1. Weight

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

6.5.2.2. Vital Signs

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

6.5.2.3. Physical Examinations

A complete physical examination will include head, ears, eyes, nose, mouth, thyroid, skin, heart and lung examinations, lymph nodes, gastrointestinal, skeletal, and neurological systems. All subsequent physical examinations should focus on signs and symptoms reported by the patient to assess for clinically significant changes from the Baseline assessment. The physical examinations at Week 52 and Week 104 will include a breast examination.

6.5.2.4. Clinical Laboratory Samples

All protocol-required laboratory assessments must be conducted in accordance with the Investigator Site File 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 Chloride Bicarbonate Blood urea nitrogen Creatinine Glucose Calcium Phosphate Magnesium Sodium Albumin Creatine kinase Hemoglobin A1c Bilirubin total Alanine aminotransferase Aspartate aminotransferase Gamma-glutamyl transferase Alkaline phosphatase	White blood cell count White blood cell differential Red blood cell count Hemoglobin Hematocrit Mean corpuscular volume Platelet count Red blood cell morphology	Protein Glucose Blood Urobilinogen Bilirubin Color and clarity pH Leucocyte esterase Ketones Nitrite Specific gravity Urine microscopy (reflex testing based on abnormal urine analysis)
Hormones	**Lipids**	**Pregnancy**
Estradiol	Total cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides	Pregnancy test (human chorionic gonadotropin)

The central laboratory will perform laboratory tests for chemistry, hematology, urinalysis, 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.

For patients with incomplete recovery of bone mineral density loss at the 6- and 12-month post-treatment follow-up visit, clinical laboratory tests should be performed (see Section 6.5.2.6). These laboratory assessments will be submitted to the central laboratory. If these laboratory assessments are scheduled to occur after the study database is locked, they will be performed at a local laboratory. The investigator will maintain a copy of the reference ranges (with the record of the reference ranges) for the laboratory or laboratories used.

6.5.2.5. Electrocardiograms

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

6.5.2.6. Bone Mineral Density

Bone mineral density is determined using DXA scanning and will be assessed at the lumbar spine (L1, L2, L3, and L4), total hip, and femoral neck (same leg within each patient) at the time points described in the Schedule of Activities (Section 1.1). The scans will be read by the central imaging laboratory in accordance with the imaging charter. Training, quality review, and readings will be done by a central radiology laboratory as described in the central radiology charter for bone mineral density.

Throughout the study, the same DXA apparatus will be used at each site and operated in the same scan mode for all scans for an individual patient and should be the same as used for the patient during the parent study (MVT-601-3101 and MVT-601-3102). The central core imaging laboratory will collect and evaluate all DXA scans for acceptability. Bone mineral density changes for individual patients will be monitored by the central imaging laboratory over the course of the study.

Determination of bone mineral density by DXA at the Early Termination visit or at the Week 104 visit and follow-up of findings will proceed according to the following rules:

Early Termination and 6-Month Post-Treatment DXA

- For patients who early terminate:
  - For Early Termination occurring **before Week 36**, DXA is not required at the Early Termination visit unless it will aid in the assessment of an adverse event or if the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. In this case, follow-up DXA is required at 6 months (± 1 month).
  - For Early Termination occurring **at or after the Week 36 visit**, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.

Most recent DXA was at the Week 24 visit: Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline;

Most recent DXA was after the Week 24 visit: Follow-up DXA is required at 6 months (± 1 month) if, on the most recent DXA scan in the open-label extension study, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.

Study Completion and 6-Month Post-Treatment DXA

- For patients who complete the open-label extension study:

  Follow-up DXA is required at 6 months (± 1 month) if, at the Week 104 visit or on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.

Note: Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.

Patients Who Have Previously Completed or Early Terminated from the Study

Patients who have previously completed or early terminated from the study prior to Protocol Amendment 3.1 may not have undergone post-treatment DXA according to the current protocol requirements. To allow for further follow-up of these patients, it is strongly recommend that attempts be made to contact the patients who met the protocol specified threshold of > 3% bone loss at or after the Week 36 DXA scan to obtain a post-study follow-up DXA scan at 6 months (± 1 month) from last dose of study drug, if such a scan has not been scheduled or performed. For patients who are already out of this 6-month window, an unscheduled post-treatment follow-up DXA scan is recommended.

12-Month Post-Treatment DXA

- If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with the parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study drug. Patients undergoing 12-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.
- If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with the parent study baseline, patients are recommended to be referred to and strongly encouraged to see a bone specialist for further evaluation or the bone loss.

  Note 1: Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.

Note 2: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan once the consultation is complete.

6.5.2.7. Endometrial Biopsy

For patients in parent study MVT-601-3101, an endometrial biopsy is performed at the Week 24 visit. If the required Week 24 biopsy is inadequate for diagnosis, it should be repeated, and a sample submitted to the central laboratory. If the second sample is inadequate, ensure an endometrial thickness has been reported from the Week 24 transvaginal ultrasound and contact the medical monitor to review the findings.

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

Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at the Week 52 and Early Termination visit for all patients. An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not indicate withdrawal from the study.

The Week 52, Week 104, and Early Termination endometrial biopsy samples will be submitted to the central laboratory. If the Week 52, Week 104, or Early Termination biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:

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

Investigators should contact the medical monitor if a patient refuses to have an endometrial biopsy at Week 52 or the Early Termination visit. Unscheduled endometrial biopsies may also be performed when medically indicated and as deemed necessary by the investigator. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy, unless urgently indicated. Additional consent is not required in this circumstance.

6.5.2.8. Status of Menstruation Recovery

If the first menstruation after the end of study treatment administration is observed before the Follow-Up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone

3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.

If the patient enrolls directly into another relugolix clinical study upon completion of the Week 104 visit, follow-up under this protocol to determine the status of menstruation recovery may not be required.

6.5.2.9. Mammogram

A mammogram will be performed at the Week 52 or Week 104/Early Termination visit (see the Schedule of Activities in Section 1.1) for patients ≥ 40 years of age at the time of the visit. If a patient had a recent mammogram per standard of care within the 6 months before Week 52 that was Breast Imaging Reporting and Data System category 1 or 2 or equivalent or had benign findings, as determined by the investigator or medical monitor, a mammogram is not required at Week 52 but should be completed by Week 104/Early Termination. If a patient turns 40 years old after the Week 52 visit has occurred, a mammogram should be performed no later than the Week 104/Early Termination visit.

All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 8) and recorded in the eCRF. The following actions will be taken depending on the reading:

- Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;
- Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;
- Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours.
- Patients who have malignant breast lesion(s) or breast carcinoma will be withdrawn from study drug treatment (see Section 4.5).

7. SAFETY CONSIDERATIONS

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

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 admitted to a hospital, independent of the duration of that hospitalization. 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 and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor regardless of causal relationship to study drug treatment.

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

7.3. Assigning Causal Relationship to Study Drug

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

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

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

CTCAE = Common Terminology Criteria for Adverse Events.

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 × ULN.

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

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

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

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

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

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

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

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 × ULN; AND
2. Total bilirubin increases to > 2 × ULN or INR > 1.5; AND
3. Alkaline phosphatase value does not reach 2 × ULN; AND
4. No alternative cause explains the combination of the above laboratory abnormalities; important alternative causes include, but are not limited to the following:
   - Hepatobiliary tract disease;
   - Viral hepatitis (eg, hepatitis A/B/C/D/E, Epstein-Barr virus);

- Exposure to hepatotoxic agents/drugs or hepatotoxins, including herbal and dietary supplements, plants, and mushrooms;
- Alcoholic hepatitis;
- Nonalcoholic steatohepatitis;
- Autoimmune hepatitis.

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

7.6. Serious Adverse Event Reporting

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

The contact information for submission of serious adverse events, adverse events of clinical interest (defined in Section 7.5), and events of overdose is available on the Safety 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 Report Form

The initial report should include:

- Study number (MVT-601-3103);
- 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 × 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 within 24 hours;
- 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 Safety Report 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.

If the patient agrees, the investigator should notify the patient's primary care physician of the pregnancy and provide details of the patient's participation in the study and treatment.

A pregnancy is to be reported to the sponsor within 24 hours of awareness by the study site personnel, using the Pregnancy 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 form, as available. Document the pregnancy in the eCRF as well.

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

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

Section 6.5.2 details the requirements for measurement of safety parameters including vital signs, physical examinations, clinical laboratory tests, ECGs, and bone mineral density.

7.10. Benefit/Risk Assessment

Adverse drug reactions (identified risks) associated with relugolix in women include nonserious events of hot flush, headache, hyperhidrosis, and loss of bone mineral density. In this protocol, relugolix will be evaluated for its benefit on 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 (corrected QT [QTc] prolongation), hepatic enzyme increases, phospholipidosis (PLD), reproductive toxicity, and metabolic and cardiovascular changes (insulin resistance, dyslipidemia, increased weight) with an increased risk of diabetes mellitus and possible increased risk of cardiovascular disease. Additionally, there are potential risks associated with the addition of estradiol/norethindrone acetate. Summaries of findings from both nonclinical and clinical studies conducted with relugolix can be found in the current version of the Investigator Brochure.

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

Table 7-2 Protocol Risk Assessment and Mitigation Strategies

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
Bone Mineral Density Reversible loss of bone mineral density is a risk of the hypoestrogenic state induced by relugolix. This risk is mitigated by the co-administration of low-dose estradiol and norethindrone acetate hormonal add-back therapy.	Exclusion criteria for a history of osteoporosis, metabolic bone disease, and prior medical therapy for low bone mineral density was included in the parent studies.	Bone mineral density will be monitored at the Week 24/Baseline, Week 36, Week 52, and Week 104/Early Termination visits with specified discontinuation and follow-up criteria and all fractures will be reported as adverse events.
Drug Interactions	Exclusion of co-administration P-glycoprotein inhibitors/inducers.	Collection of adverse events.

Potential Risk of Clinical Significance	Mitigation Strategy	
	Impact on Eligibility	**Monitoring and Withdrawal Criteria**
QTc Prolongation Negative Thorough QT/QTc clinical study.	Empiric exclusion of baseline QTcF > 470 msec in the parent studies.	12-lead ECG at the Week 24/Baseline and Week 52visits, and as clinically applicable; withdrawal for QTcF > 500 msec.
Hepatic Enzymes Isolated increases in hepatic transaminases have been observed in prior clinical studies. There have been no reported cases consistent with drug-induced liver injury including an increase in bilirubin. Abnormal liver test results are considered adverse events of clinical interest in this study.	Exclusion criteria for AST and ALT > 2 × the ULN; total bilirubin values > 1.5 × ULN.	Abnormal liver test results (AST or ALT > 3 × ULN) that develop during the Open-Label Treatment Period will be reported within 24 hours of study personnel awareness.
Phospholipidosis Data from nonclinical studies in rats and monkeys showed histopathological changes consistent with PLD. PLD by itself is not adverse. No clinical evidence of relugolix-related PLD-associated toxicity has been observed nor was there a clinically meaningful increase in a biomarker of PLD assessed in phase 2 clinical studies.	Patients with significant underlying medical conditions are excluded.	Routine safety monitoring including laboratory assessments, ECGs, and assessment of adverse events, including any ophthalmologic adverse events, will be monitored during this study.
Metabolic Changes Metabolic changes (insulin resistance, dyslipidemia, and increased weight) with increased risk of diabetes are a potential risk of the hypoestrogenic state induced by relugolix.	Exclusion criteria for current medical history of cardiovascular disease in the parent studies.	Fasting lipids and glucose will be monitored during the study.
Reproductive Toxicity	Premenopausal compliance with specified acceptable non-hormonal contraception; exclusion of pregnant and lactating women.	Pregnancy testing at each study visit; immediate withdrawal for pregnancy.

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) Low-dose estradiol and norethindrone acetate are approved for the prevention of postmenopausal osteoporosis and the treatment of moderate to severe vasomotor symptoms. It is contraindicated for women with a history of breast cancer or estrogen-dependent neoplasia, history of (or active) deep vein thrombosis, pulmonary embolism, thromboembolic disease (myocardial infarction or stroke within the past year), liver dysfunction, prior hypersensitivity, and pregnancy.	Women with breast cancer or other estrogen-dependent malignances, a history of deep vein thrombosis, pulmonary embolism, thromboembolic disease, liver dysfunction, prior hypersensitivity, migraine with aura, porphyria, and pregnancy excluded from the parent studies. Physical examination, clinical chemistries, and 12-lead ECG will be performed at the Week 24/Baseline visit.	Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each study visit; A mammogram will be performed at Week 52 or at the Week 104/Early Termination visit for women who are or become ≥ 40 years old during the study, with specified discontinuation criteria. Adverse events will be recorded.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; QTc = corrected QT interval; QTcF = QT interval by the Fridericia correction; PLD = phospholipidosis; ULN = upper limit of normal.

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 Investigator Site File 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 (SAP) will describe the detailed statistical methods and analyses for this study.

All efficacy and safety measures over the course of both the parent and extension studies will be presented by the parent study treatment group using descriptive statistics. No formal treatment comparisons will be performed for this extension study. Continuous data will be summarized by means, standard deviations, medians, maximum, minimum, and number of patients. Categorical data will be summarized by counts and percentages.

There will be two analyses: one at Week 52 and one at Week 104. A clinical study report will be generated from each analysis.

The study may be closed pending selected contingent safety procedures conducted after the last patient's Week 104/Early Termination or Follow-Up visit. After the study is closed, any pending required follow-up testing of bone mineral density and endometrial biopsies or for menstruation recovery beyond the Follow-Up visit will be captured and reported.

9.1. Randomization Methods

This is a single-arm, open-label extension study; patients are not randomized. All patients who have entered the extension study will be treated with open-label relugolix and low-dose hormonal add-back therapy for 80 weeks.

9.2. Analysis Populations

Efficacy data analyses will be performed on the Extension Study Population, defined as all patients who enrolled into MVT-601-3103 and who have received any amount of randomized open-label study drug in MVT-601-3103.

Safety data analyses will be performed on the Safety Population, defined as all enrolled patients who have received any amount of MVT-601-3103 study drug.

The analysis methods for safety and efficacy endpoints are the same as those used for the parent studies, unless otherwise specified in the SAP.

9.3. Sample Size Justification

Because this is an extension study, the sample size will be determined by the number of patients who have completed a parent study and who are eligible and willing to participate in the extension study. It is estimated that approximately 800 patients (67% of the total of 1200 patients who will be randomized into the parent studies) will participate in this study.

9.4. Efficacy Analyses

Unless otherwise specified, efficacy analyses will be conducted using the Extension Study Population.

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

The point estimates and 2-sided 95% confidence intervals (CI) for the primary efficacy endpoints (proportion of responders based on dysmenorrhea NRS scores and use of rescue analgesic medications, proportion of responders based on NMPP scores and use of rescue analgesic medications) will be calculated.

A responder at a given time point and for a specific type of pain (dysmenorrhea or NMPP) is defined as a patient who had a reduction in that type of pain from Baseline in the parent study greater than or equal to a pre-determined threshold and who did not have an increase in the use of rescue analgesic medications for endometriosis-associated pain compared with the use at Baseline. Patients who had a pain reduction less than the pre-determined threshold or who had an increase in the use of analgesics for endometriosis-associated pain will be considered non-responders. The pain reduction thresholds will be determined for NMPP and dysmenorrhea separately (see the SAP for details) for the parent studies and these same thresholds will be applied to this study.

Baseline values are calculated using the Baseline pain assessment period, which is defined as the period from the date of the first dose of placebo in the parent study Run-In Period through the day prior to the first dose of randomized study drug. Patients' average NRS pain scores and use of rescue analgesic medications for endometriosis-associated pain (dysmenorrhea or NMPP) will be compared between a given visit-specific pain assessment period (eg, Week 28, Week 32, etc.) and the Baseline pain assessment period. The visit-specific pain assessment period is defined as the last 35 calendar days immediately prior to and including the last dose of study drug treatment received prior to the visit date.

For any pain assessment period (Baseline or visit-specific), the average NRS scores will be calculated for dysmenorrhea and NMPP separately. An average NRS score for dysmenorrhea is calculated as the average NRS score over the days with menses during a given pain assessment period. An average NRS score for NMPP is calculated as the average NRS score over the days without menses during a given pain assessment period. The analgesic use for a given pain assessment period is summarized by total dose count defined as the average daily dose count taken during the given pain assessment period multiplied by 35. Additional details on calculating dose counts and on the precise definition of an increase in analgesic use will be provided in the SAP.

Descriptive statistics will be provided for efficacy endpoints (listed below) similar to those used for the parent studies at Week 52 and Week 104.

- Change from the parent study Baseline in the EHP-30 Pain Domain scores;
- Change from the parent study Baseline to in the mean dysmenorrhea NRS score;
- Proportion of patients who are better or much better on the PGIC for dysmenorrhea;
- Change from the parent study Baseline in the mean NMPP NRS score;
- Change from the parent Baseline in the mean NRS score;
- Proportion of patients not using opioids;
- Proportion of patients not using analgesics;
- Proportion of patients who are better or much better on the PGIC for NMPP;

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

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

For endpoint of proportion of responders based on EHP-30 Pain Domain scores, a responder is defined using the same within-patient score change threshold determined from the parent studies.

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

9.5. Safety Analyses

Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA, mammograms (for patients required to have this procedure, see Section 6.5.2.9), and endometrial biopsy. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.

The treatment-emergent period will be defined as the period of time from the first dose date and time of randomized study drug in the parent study 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, 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, high level term, and system organ class using MedDRA 20.0 or higher. The incidence of adverse events will be presented by MedDRA system organ class and preferred term, relationship to study drug treatment, and severity. A patient reporting the same adverse event more than once is counted

once, and at the maximum severity or strongest relationship to study drug treatment when calculating incidence.

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

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

Clinical laboratory data consist of chemistry, hematology, and hormonal tests. Only data collected by the central laboratory will be used to do the analyses. Electrocardiograms will also be read centrally. The distributions of QTc interval will be summarized at each visit. All data will be listed and summarized by visit. The change from parent study Baseline to each post-baseline study visit will be presented by treatment group for each ECG parameter.

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

Bone mineral density data will be collected and analyzed by the central radiology laboratory including bone mineral content (g), bone area (area, cm^2), and bone mineral density (g/cm^2) each for L1, L2, L3, L4, total hip, and femoral neck, and average bone mineral density of L1-L4 (lumbar spine), Z-score for bone mineral density lumbar spine (L1-L4), total hip, and femoral neck.

For the relugolix add-back treatment Group A, the lower bound of the 95% CI for (arithmetic) mean percentage change at Week 52 from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be compared with a pre-specified clinically acceptable threshold of -2.2% to evaluate magnitude of bone mineral density loss after 52 weeks of treatment. If the lower bound is > -2.2%, the bone mineral density loss for the relugolix add-back treatment will be considered insignificant. As supportive analysis, least square means and 95% CI for percent change at Week 52 from parent study Baseline in bone mineral density will be provided based on mixed effects model (assumed missing at random) for each parent study treatment group. The 95% CI for mean percentage change at Week 104/Early Termination from parent study Baseline in bone mineral density lumbar spine (L1-L4) will be provided along with descriptive statistics for bone mineral density loss at Week 104/Early Termination as supportive analyses.

All data will be listed and summarized by visit. The absolute change and percent change from parent study Baseline to Weeks 36, 52, and 104/Early Termination and associated 95% CIs will be presented by the parent study treatment group for each bone mineral density parameter. The number and percentage of patients meeting a bone mineral density decline of at least 4%, 5%, 6%, or 7% by body area (lumbar spine, total hip, or femoral neck) will be estimated with 95% CIs by the parent study treatment group.

Additional analyses will be performed to examine the correlation between bone mineral density loss with demographic and baseline characteristics and with treatment exposure. Details will be provided in the SAP.

9.6. Pharmacodynamics Analyses

The change from the parent study Baseline to Week 52 and to Week 104 in predose concentrations of serum estradiol will be summarized. Percentage of patients with concentrations of serum estradiol levels < 10 pg/mL and < 20 pg/mL will be provided.

9.7. Exploratory Analyses

Descriptive summaries by treatment group will be provided for the following exploratory endpoints. Details on the endpoint analyses including deviations, handling of missing data, and statistical methods will be provided in the SAP. The following exploratory endpoints will be assessed at Week 52 and Week 104:

- Change from Baseline in the EHP-30 scale total score;
- Change from Baseline in the EHP Work Domain score;
- Change from parent study Baseline in the EQ-5D-5L.

9.8. Interim Analyses

An interim analysis will be conducted at Week 52 in which all efficacy and safety endpoints will be assessed as described above. A clinical study report will be generated based on these data to support submission of one-year data.

9.9. Steering Committee

The study will be overseen by a Steering Committee consisting of experts in the field of women's health and staff members of Myovant Sciences GmbH. The Steering Committee will participate in the design, conduct, analyses, and publication of the study.

10. RESPONSIBILITIES

10.1. Investigator Responsibilities

10.1.1. Good Clinical Practice

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

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

10.1.2. Institutional Review Board/Independent Ethics Committee Approval

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

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

10.1.3. Informed Consent

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

signed and dated by the patient 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, US, 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 Investigator Site File. 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 lot numbers) of all used and unused study drug (active and placebos). This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, accountability, and returned or destroyed study

product. Dispensing records will document quantities received from the sponsor and quantities dispensed to patients, including lot number, date dispensed, Patient 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, European Union (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. All protocol modifications must be submitted to the IRB or IEC in accordance with local requirements. Approval must be obtained before changes can be implemented. The investigator must not deviate from the protocol without first obtaining approval from the sponsor and the IRB or IEC, if required. In medical emergencies, the investigator will use medical judgment and will remove the patient from immediate hazard, then notify the sponsor (or designee) and the IRB or IEC immediately regarding the type of emergency and the course of action taken. The investigator must notify the sponsor (or designee) of any inadvertent protocol deviations upon their discovery and document the deviations appropriately in the study files.

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

10.2.3. Study Report

A clinical study report will be prepared and provided to the regulatory authority(ies) at Week 52 and a second clinical study report will be prepared at the end of the study (Week 104). 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). 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.

11. REFERENCES

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12. APPENDICES

Appendix 1. 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)
- Tier 2[1]
  - 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).

Appendix 2. Daily eDiary

Version 3 MY80005-eDiary
US English Screen Report 23May2017

Screen report: my80005-eDiary Subject Facing

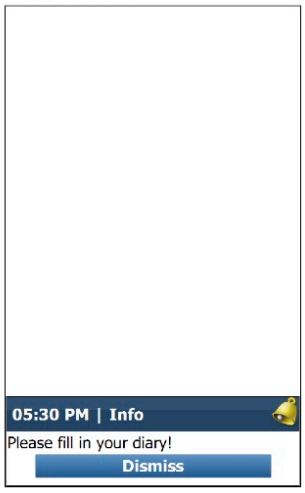
Localized texts are displayed in English.

Contents

Version 3
US English Screen Report

MY80005-eDiary
23May2017

1 Common

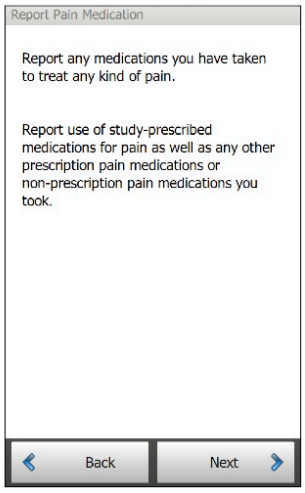


Message 1

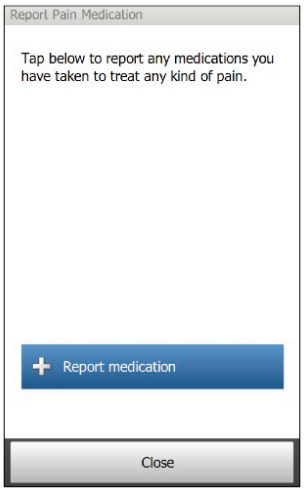
Note: Time will populate per device

Version 3 MY80005-eDiary
US English Screen Report 23May2017

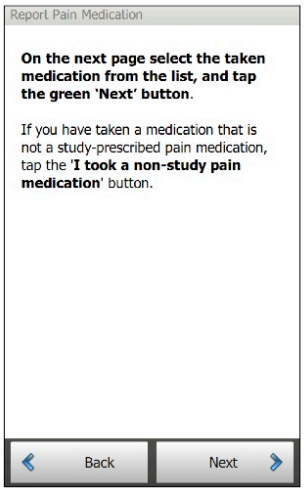
2 Form: MedReport



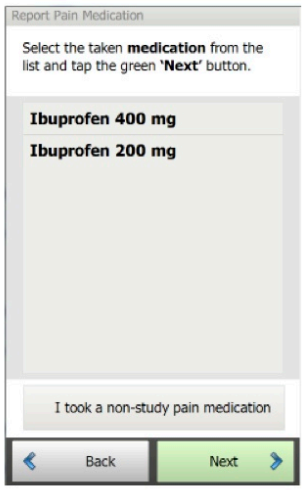
Screen 1



Screen 2



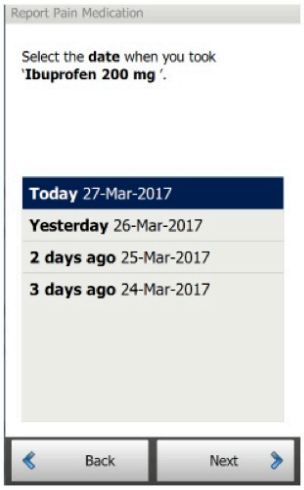
Screen 3



Screen 4

Note: Medications will show per patient set up

Message 1



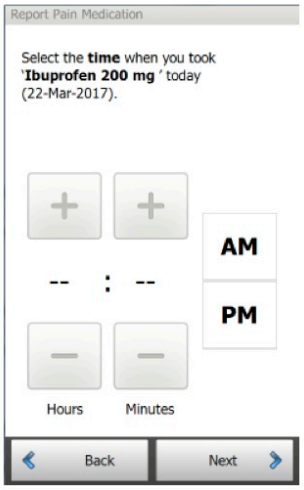
Screen 5

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

Version 3
US English Screen Report

MY80005-eDiary
23May2017

Message 2

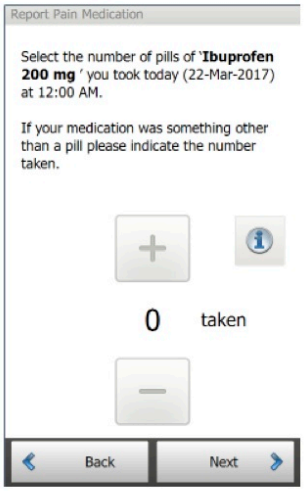


Screen 6

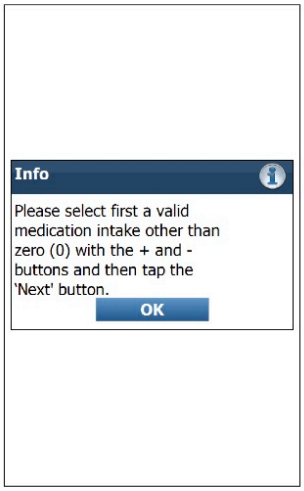
Message 3

Note: Medication Name and Date will show per device

Message 4



Screen 7

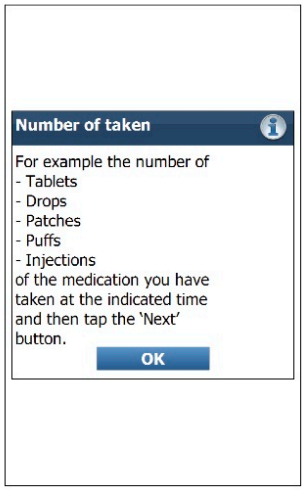


Message 5

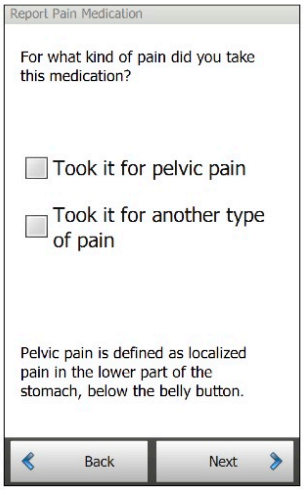
Note: Medication Name and Date and time will show per device

Version 3
US English Screen Report

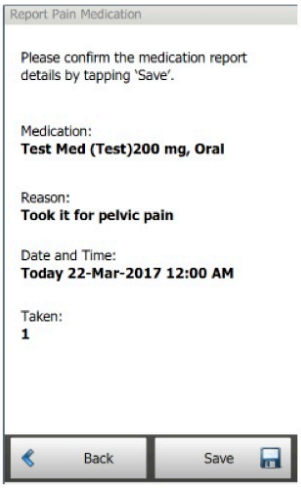
MY80005-eDiary
23May2017



Message 6

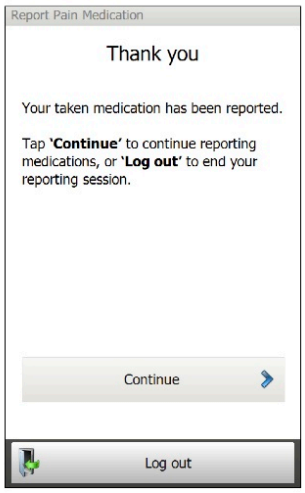


Screen 8



Screen 9

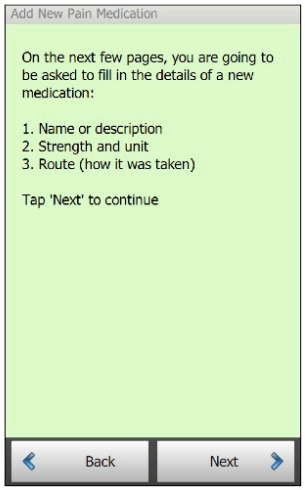
Note: 'Medication', 'Reason', 'Date and Time', 'Taken' will show per patient selection



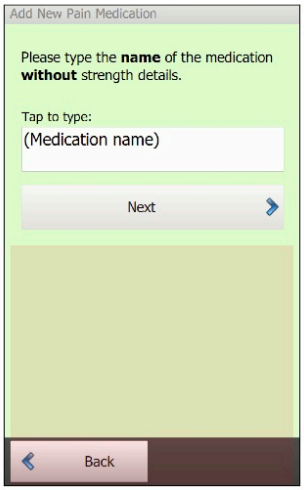
Screen 10

Version 3
US English Screen Report

MY80005-eDiary
23May2017

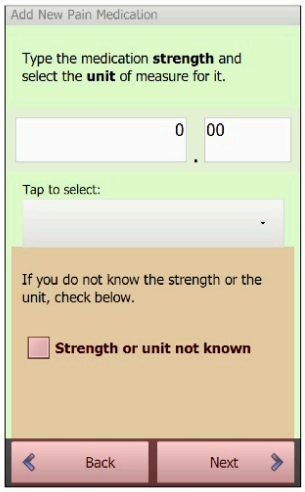


Screen 11



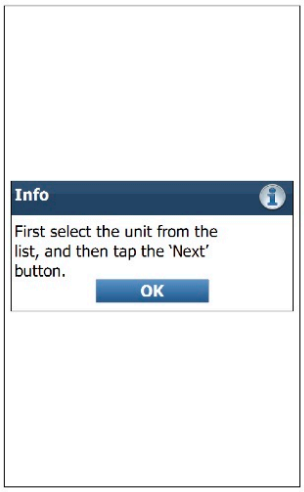
Screen 12

Message 7



Screen 13

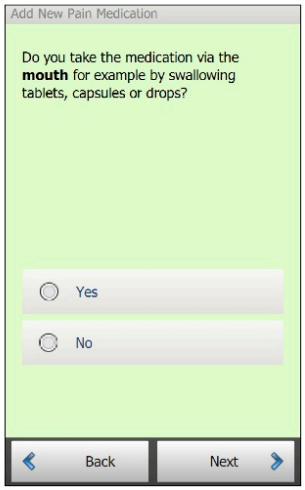
Message 8



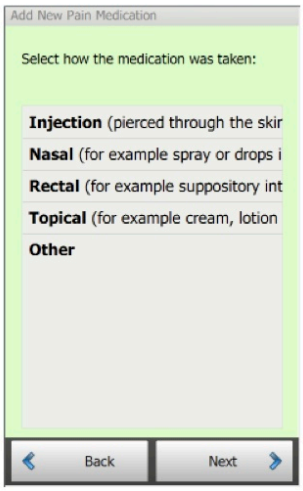
Message 9

Version 3
US English Screen Report

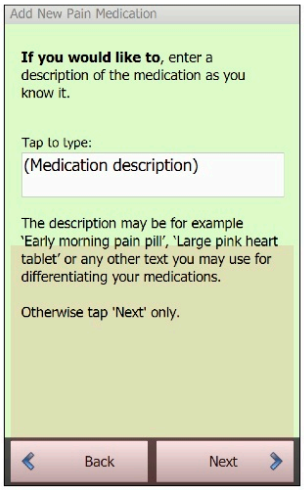
MY80005-eDiary
23May2017



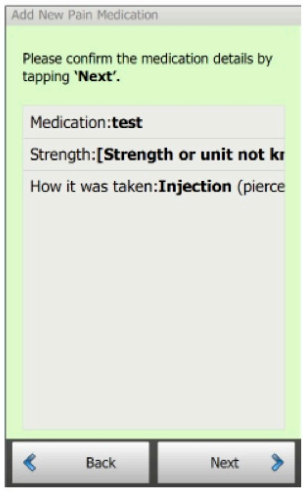
Screen 14



Screen 15



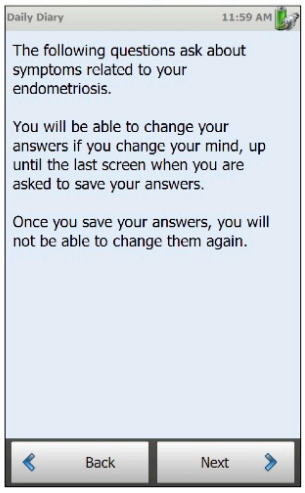
Screen 16



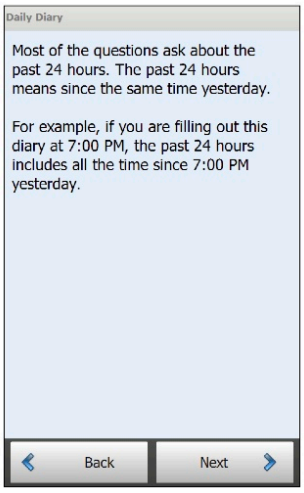
Screen 17

Version 3 MY80005-eDiary
US English Screen Report 23May2017

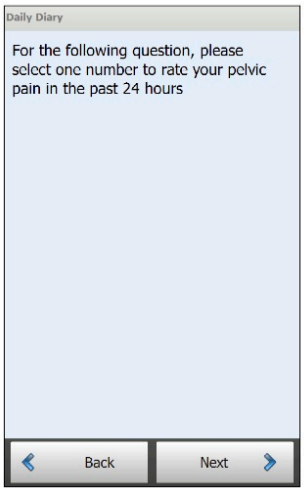
3 Form: Daily Diary



Screen 1



Screen 2



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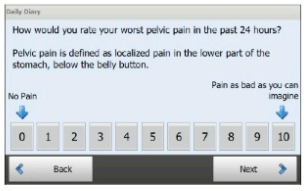
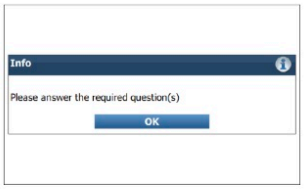


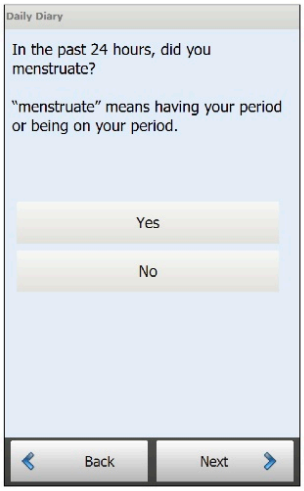
Screen 4

Note: Screen will show latteraly on device



Message 1

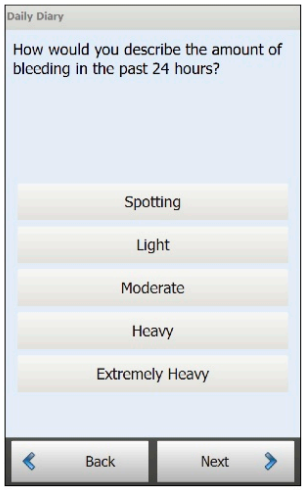
Note: Screen will show latteraly on device



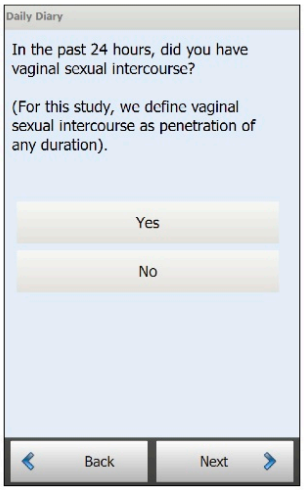
Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017



Screen 6



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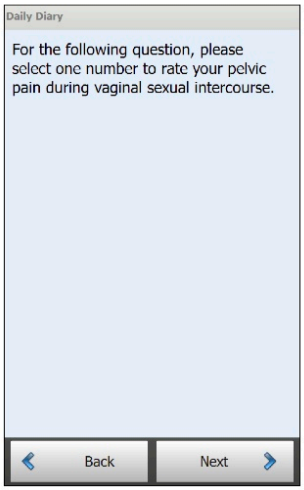
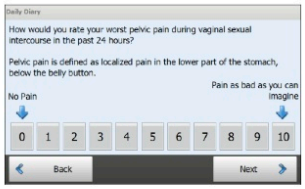
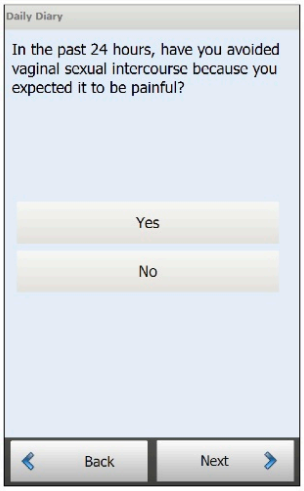


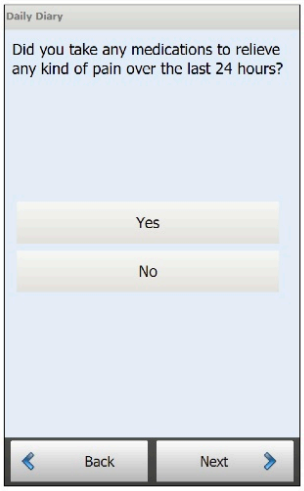
Screen 8



Screen 9



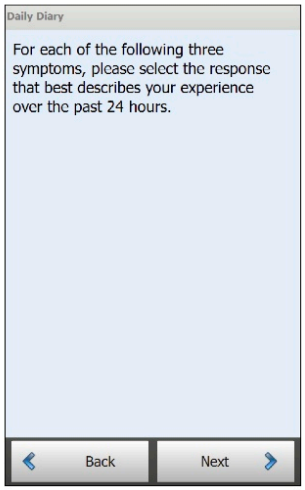
Screen 10



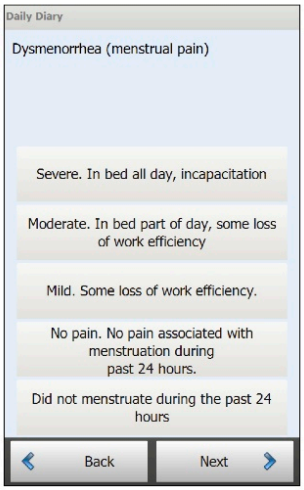
Screen 11

Version 3
US English Screen Report

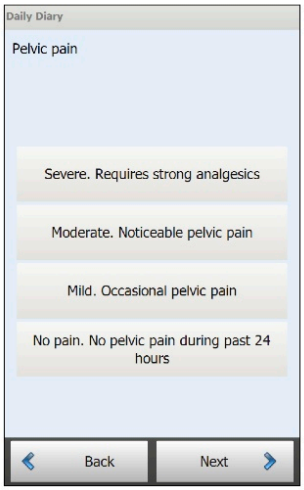
MY80005-eDiary
23May2017



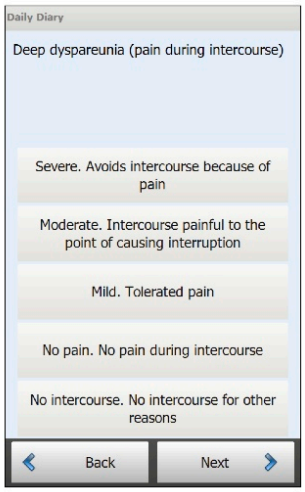
Screen 12



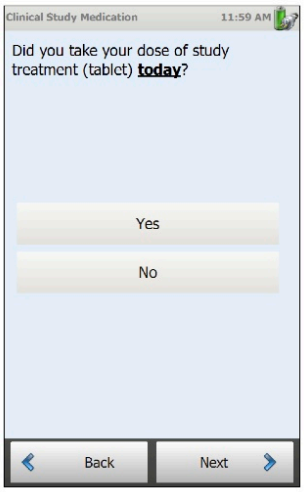
Screen 13



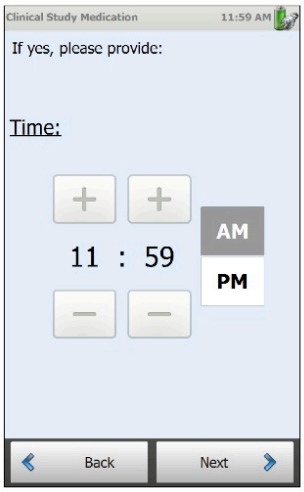
Screen 14



Screen 15



Screen 16

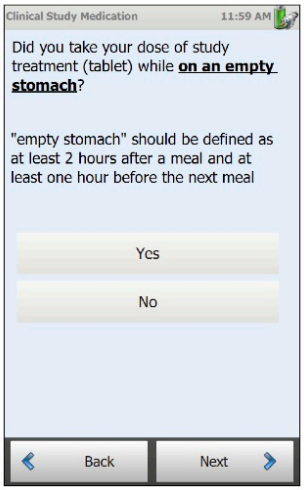


Screen 17

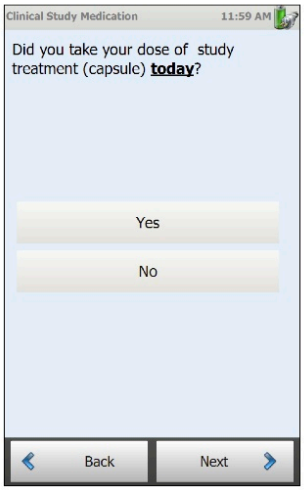
Version 3
US English Screen Report

MY80005-eDiary
23May2017

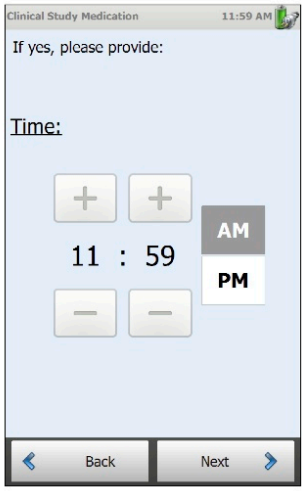
Message 2



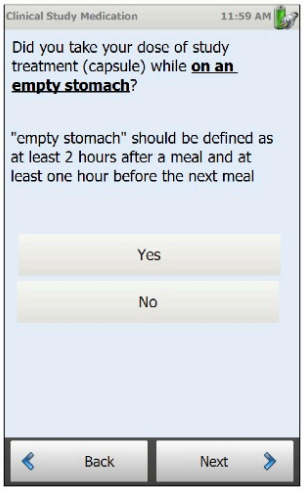
Screen 18



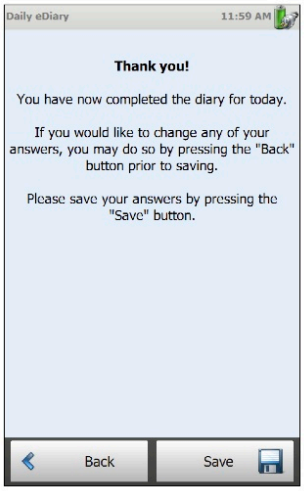
Screen 19



Screen 20



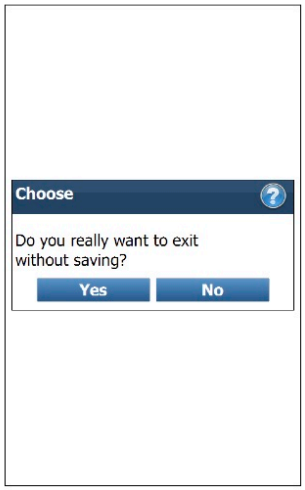
Screen 21



Screen 22

Version 3
US English Screen Report

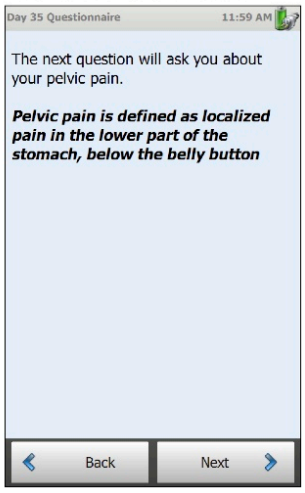
MY80005-eDiary
23May2017



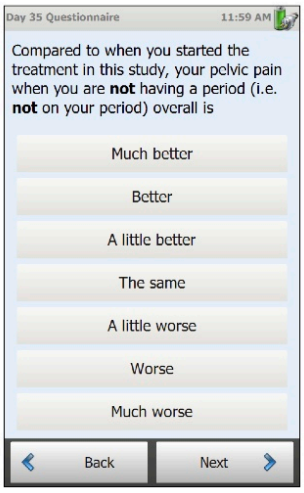
Message 1

Version 3 MY80005-eDiary
US English Screen Report 23May2017

4 Form: PGIC-NMPP

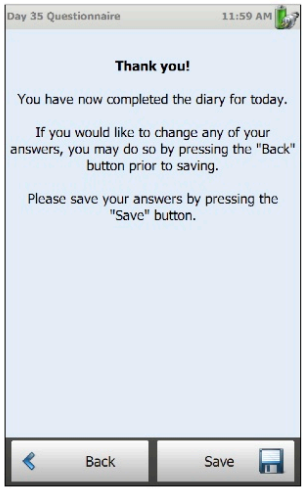


Screen 1



Screen 2

Message 1

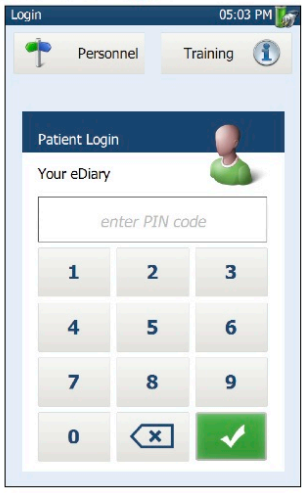


Screen 3

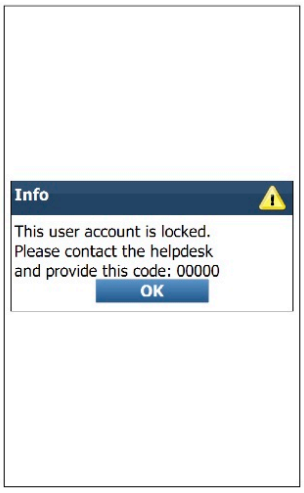
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

5 Form: Login



Screen 1

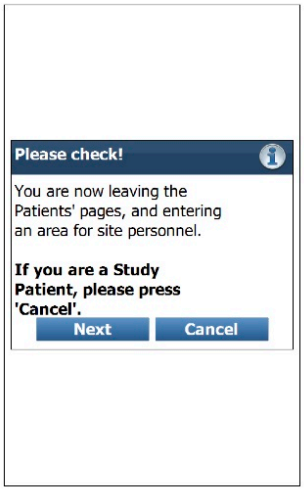


Message 1

Message 2

Message 3

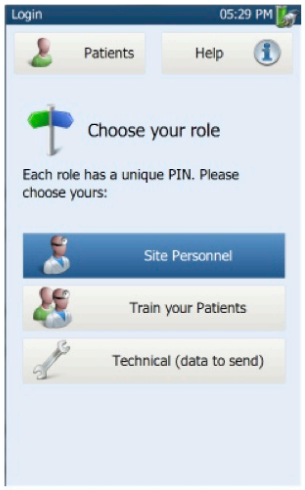
Message 4



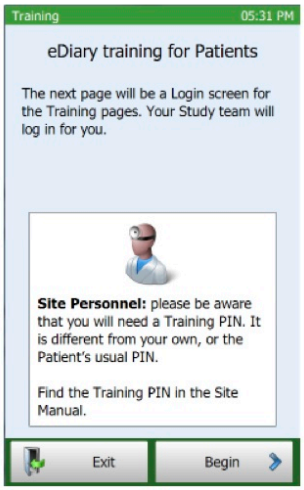
Message 5

Version 3
US English Screen Report

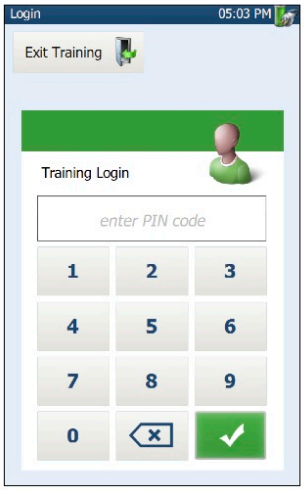
MY80005-eDiary
23May2017



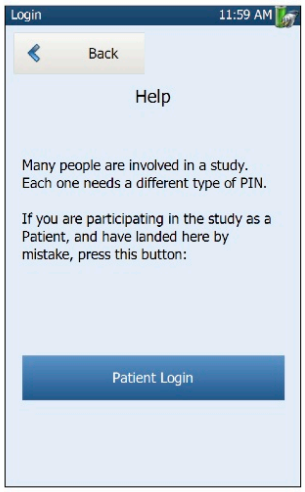
Screen 2



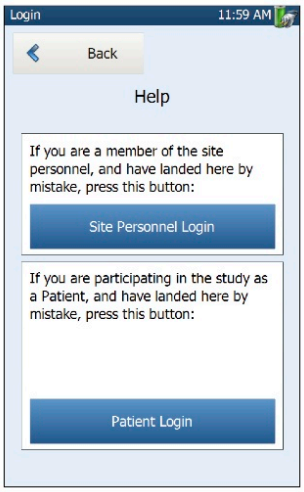
Screen 3



Screen 4



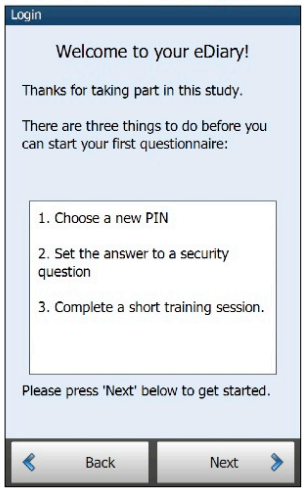
Screen 5



Screen 6

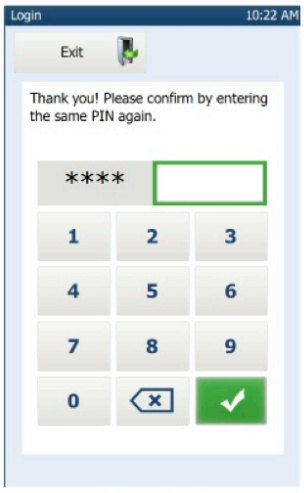
Version 3 MY80005-eDiary
US English Screen Report 23May2017

6 Form: PIN change



Screen 1

Screen 2



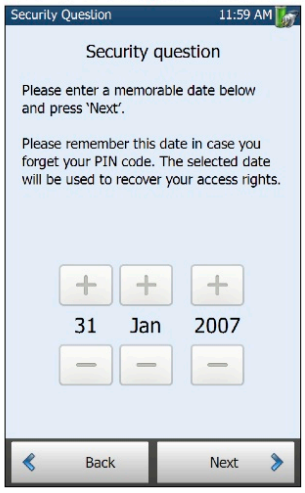
Screen 3

Message 1

Version 3
US English Screen Report

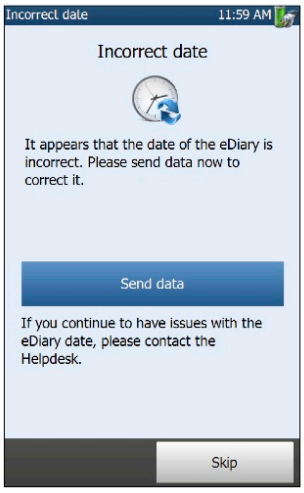
MY80005-eDiary
23May2017

7 Form: Subject main menu

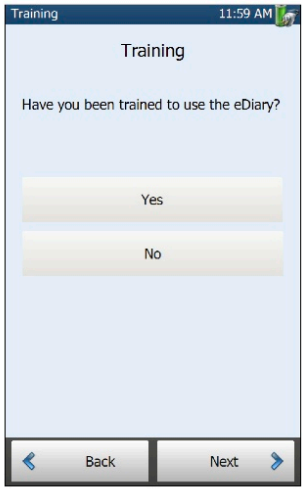


Screen 1

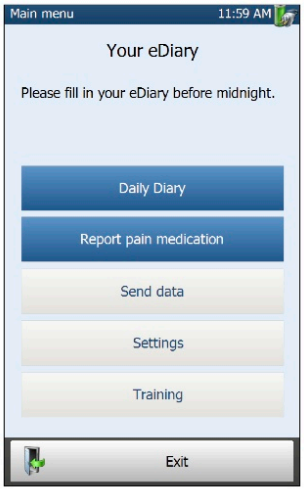
Message 1



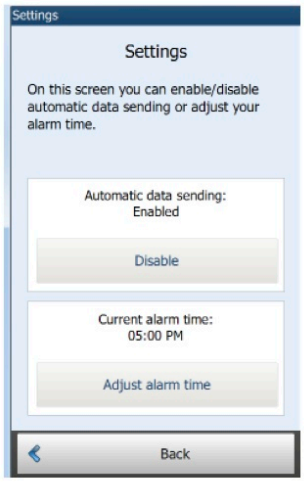
Screen 2



Screen 3



Screen 4



Screen 5

Note: Time will update per device

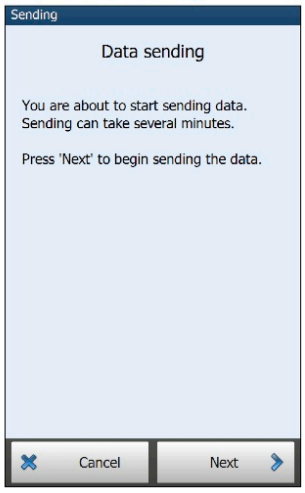
Version 3
US English Screen Report

MY80005-eDiary
23May2017

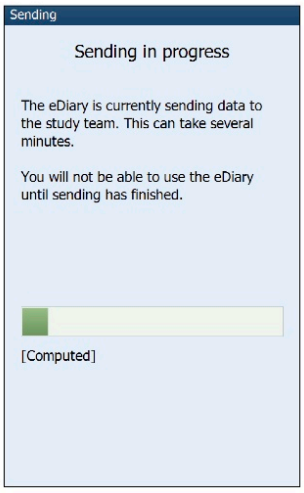
Message 2

Version 3 MY80005-eDiary
US English Screen Report 23May2017

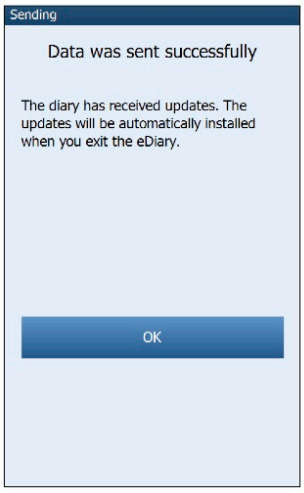
8 Form: Sending



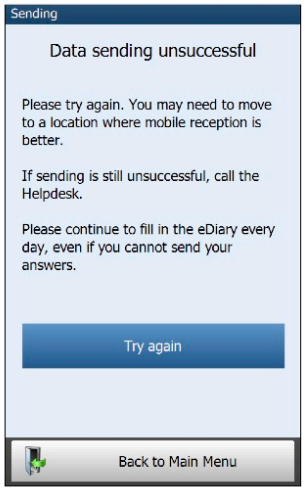
Screen 1



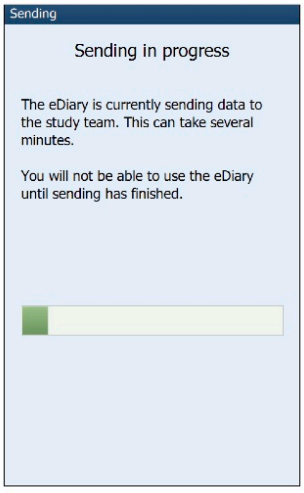
Screen 2



Screen 3



Screen 4

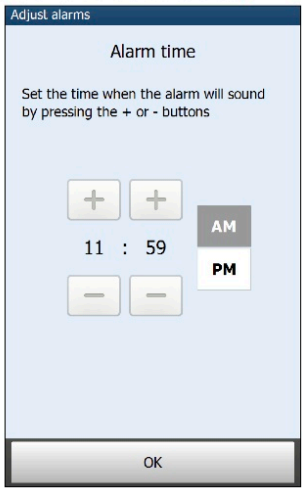


Screen 5

Version 3
US English Screen Report

MY80005-eDiary
23May2017

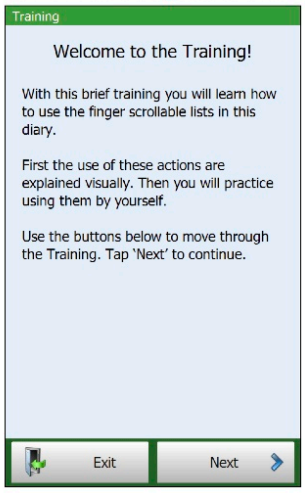
9 Form: AlarmSetup



Screen 1

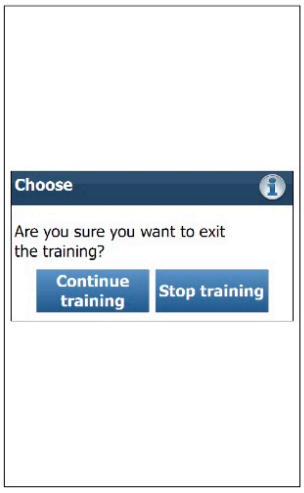
Version 3 MY80005-eDiary
US English Screen Report 23May2017

10 Form: Subject training diary

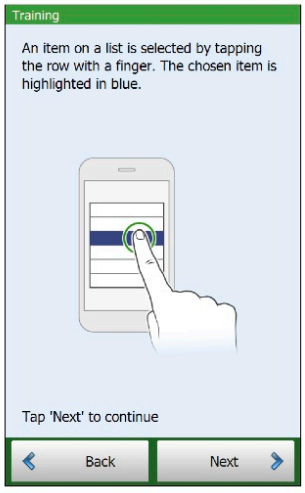


Screen 1

Message 1

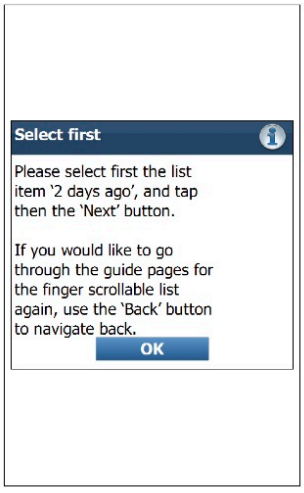


Message 2



Screen 2

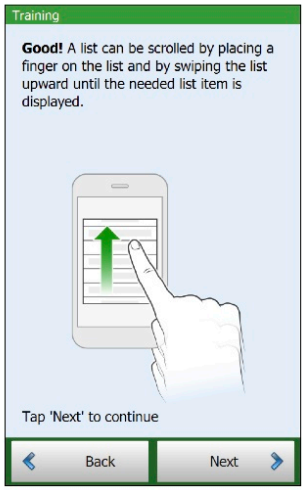
Screen 3



Message 3

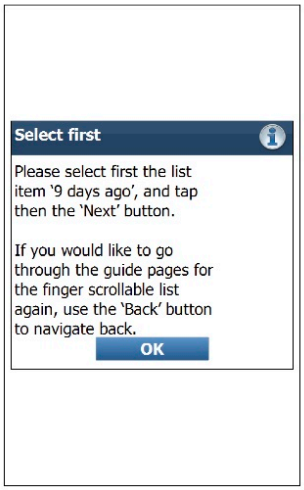
Version 3
US English Screen Report

MY80005-eDiary
23May2017

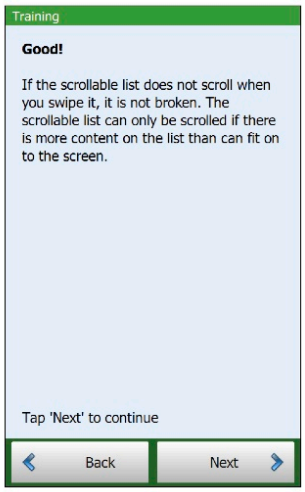


Screen 4

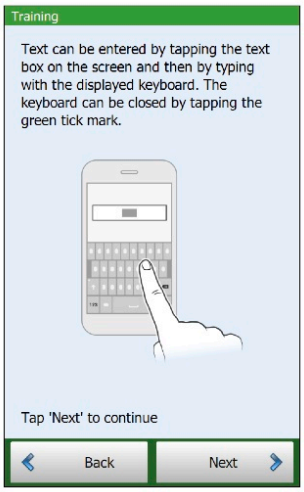
Screen 5



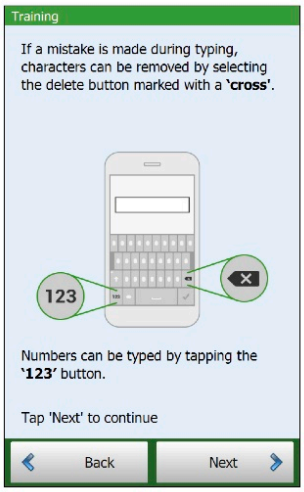
Message 4



Screen 6



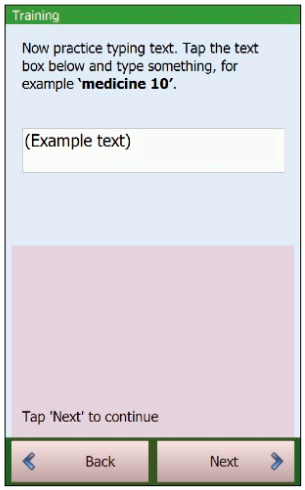
Screen 7



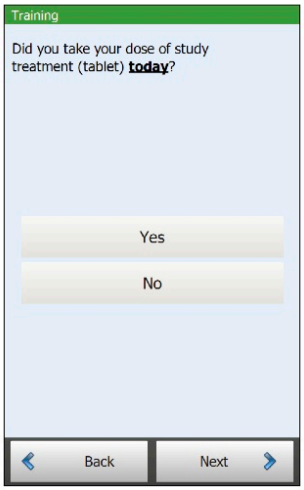
Screen 8

Version 3
US English Screen Report

MY80005-eDiary
23May2017

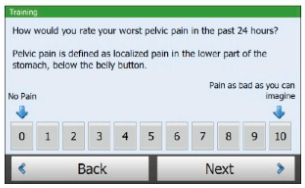


Screen 9



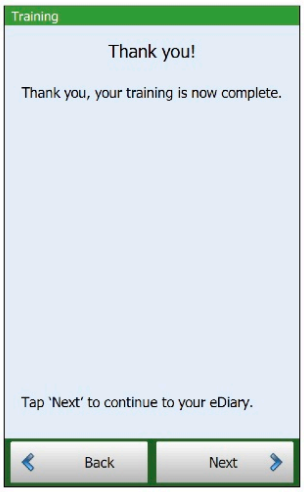
Screen 10

Message 5



Screen 11

Note: Screen will show latteraly on device



Screen 12

Version 3
US English Screen Report

MY80005-eDiary
23May2017

11 Keyboards

Appendix 3. 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 4. 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 ❑

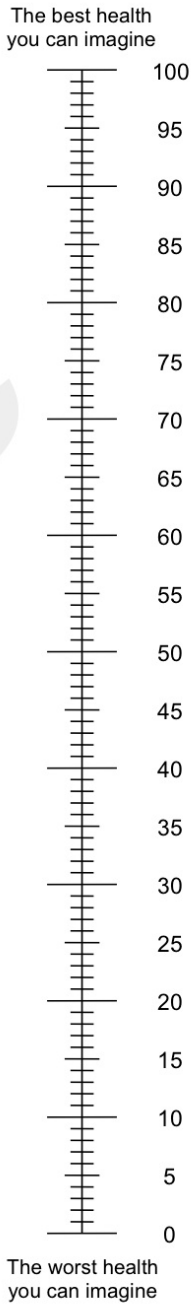
ANXIETY / DEPRESSION

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 5. 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

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

- Not at all
- Minimally
- Moderately
- Significantly
- Very significantly

Note: PGA for function is administered via a paper questionnaire.

Appendix 6. Endometriosis Health Profile - Work Domain

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.***

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

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

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

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

Appendix Table 2 Investigations of Alternative Causes for Abnormal Liver Tests

Obtain a detailed history and perform a physical examination:

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

Recommended tests:

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

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

CBC = complete blood count; INR = international normalized ratio.

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. 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 9. Guidance for Study Conduct during the COVID-19 Pandemic

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

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

Safety During the COVID-19 Pandemic

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

Protocol Adherence

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

Visit Schedules and Study Procedures

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

If a clinical study site remains open for on-site patient visits, patients should be encouraged to return for study visits, if willing and able, in the earliest allowable portion of the visit window, taking all measures to prevent contracting COVID-19.

- All protocol required study procedures should be performed whenever possible.
- Safety assessments should be prioritized if only limited assessments are performed.
- If assessments are limited, investigators should document whether the assessments performed are adequate to ensure it is safe for the patient to continue in the study.

- Investigators should use all available information to determine whether in-person visits are necessary to fully assure the safety of study patients (for example to carry out procedures necessary to assess safety or the safe use of the study drug appropriately) or whether alternative means of assessment are adequate to assure the safety of continuing patients in the study. Such decisions should be documented. Investigators can contact the medical monitor for consultation as necessary.

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

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

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

As soon as the study patients are able to return to the investigational site for an on-site visit, they should return either for their next scheduled visit (if still within protocol window) or for an unscheduled visit (if outside of expected protocol visit window).

Study Participant Study Drug Supply

If a regional lockdown, travel restrictions, or site closure is imminent due to the COVID-19 pandemic, sites are encouraged to dispense additional study drug at an expected study visit or request patients to return for an unscheduled visit for additional study drug dispensation so patients have sufficient supply until their next upcoming visit. Patients should be instructed to

contact the site to report any medical issues they may experience and site staff should communicate with the patients to determine if it is appropriate for the patient to continue dosing with study drug if/when in-person study visits are not possible.

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

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

Onsite Study Monitoring Restrictions

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

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

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

- FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency Guidance for Industry, Investigators, and Institutional Review Boards (March 2020 – updated July 2, 2020);
- European Medicines Agency Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic (Version 3, 28 April 2020).

AMENDMENT 3.1: SUMMARY OF CHANGES

The MVT-601-3103 clinical study protocol has been amended as described in the table below. The primary purpose of the amendment is to include a mammogram at Week 52 or Week 104/Early Termination for women ≥ 40 years old and to revise the threshold for post-treatment follow-up in order to assess the trajectory of BMD recovery in patients with a lesser degree of BMD loss.

A detailed list of changes is described below, where deleted text is indicated by ~~strikethrough~~ and new text is indicated with **bold** formatting. Note that the correction of typos, minor clarifications, and minor wording changes to improve readability, understanding, and consistency may not be included in this table.

Section Item	Original	Amendment 3.1	Rationale
Title Page	Amendment 2: 11 Dec 2018	Amendment 2: 11 Dec 2018 **Amendment 3.1: XX Aug 2020**	Added current version and date.
Sponsor Signature Page	Protocol Number: MVT-601-3103 Amendment ~~2~~	Protocol Number: MVT-601-3103 Amendment **3.1**	Updated amendment number.
List of Abbreviations		**COVID-19 novel coronavirus 2019**	Added new abbreviation.
List of Abbreviations		**DTP direct-to-patient**	Added new abbreviation.
List of Abbreviations		**SDV source data verification**	Added new abbreviation.
1. Synopsis Secondary Efficacy Objectives	• Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; • PGIC for NMPP;	• Nonmenstrual pelvic pain (NMPP), as measured by the NRS for NMPP; • **Overall pelvic pain, as measured by the NRS;** • **Analgesic use;** • PGIC for NMPP;	Included additional objectives to evaluate pelvic pain and analgesic use.
1. Synopsis Study Design	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density with DXA.	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, **mammograms (for patients required to have this procedure, see Section 6.2.5.9), endometrial biopsies,** and bone mineral density with DXA.	To assess patients' safety while on estradiol and norethindrone, mammogram is added for patients 40 years of age or older.
1. Synopsis Study Design	Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed according to the following rules: ~~• For Early Termination occurring between Week 24 and Week 52:~~ – For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event. ~~Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone~~	Determination of bone mineral density by DXA at the Early Termination **or the Week 104 visit** and follow-up of findings will proceed according to the following rules: **Early Termination and 6-Month Post-Treatment DXA** **For patients who Early Terminate:**	Clarified follow-up procedures for bone mineral density loss. Lowered threshold for post-treatment follow-up in order to assess the trajectory of BMD recovery in patients with a lesser degree of BMD loss.

Section Item	Original	Amendment 3.1	Rationale
	~~mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.~~ – For Early Termination occurring after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination. Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline. Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. ● ~~For Early Termination occurring between Week 52 and Week 104:~~ – ~~DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.~~ – ~~Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar~~	○ For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event **or if the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. In this case, follow-up DXA is required at 6 months (± 1 month)**. ○ For Early Termination occurring at or after the Week 36 visit, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination. ○ **Most recent DXA was at the Week 24 visit**: Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline. ○ **Most recent DXA was after the Week 24 visit:** Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. ○ **Study Completion and 6-Month Post-Treatment DXA**	

Section Item	Original	Amendment 3.1	Rationale
	~~spine (L1-L4) or total hip was > 7%, relative to parent study baseline.~~	• **For patients who complete the open-label extension study:** ○ **Follow-up DXA is required at 6 months (± 1 month) if, at the Week 104 visit or on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.** Note: Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous. **12-Month Post-Treatment DXA** • **If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with the parent study baseline, patients are strongly encouraged to come back to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study drug. If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the lumbar spine and/or total hip compared with parent study baseline, patients are recommended to be referred to and strongly encouraged to see a bone	

Section Item	Original	Amendment 3.1	Rationale
		specialist for further evaluation of the bone loss. **Note: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan after the consultation is completed.**	
1. Synopsis Study Design	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.**	Clarified procedures for when a patient is lost to follow-up that a certified letter should be sent to ensure every effort is made to contact patients
1. Synopsis Criteria for Evaluation		• Change from the parent Baseline in the mean NRS score; • Proportion of patients not using opioids; • Proportion of patients not using analgesics;	Added to align with analyses conducted for the parent studies to evaluate analgesic use and overall pelvic pain.
1. Synopsis Statistical Methods	Efficacy data will be summarized by the original randomized treatment group assigned in the parent study (ie, Parent Study Groups A, B, and C) for the ~~modified Intent-to-Treat~~ Population.	Efficacy data will be summarized by the original randomized treatment group assigned in the parent study (ie, Parent Study Groups A, B, and C) for the **Extension Study** Population.	Corrected name of population.

Section Item	Original	Amendment 3.1	Rationale
	Safety Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, and bone mineral density with DXA.	Safety Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA**, mammograms (for patients required to have this procedure, see Section** Error! Reference source not found.**), and endometrial biopsy.**	Added mammogram for patients who are ≥ 40 years of age.
1.1. Schedule of Activities 12-Lead ECG Week 104/Early Termination		**X[h]**	Added ECG at Week 104/Early Termination visit.
1.1. Schedule of Activities Clinical Laboratory Tests during Safety Follow-up		X[ee]	Added clinical laboratory tests during follow-up period since they may be included as part of bone densitometry follow-up.
1.1. Schedule of Activities Bone Densitometry during Safety Follow-up		**X[ee]**	Added bone densitometry follow-up.
1.1. Schedule of Activities Endometrial Biopsy during Safety Follow-up		**X[ee]**	Added endometrial biopsy follow-up.
1.1. Schedule of Activities Status of Menstruation Recovery during Safety Follow-up	X[bb]	X[bb,ee]	Added clarifying footnote for status of menstruation recovery during safety follow-up.

Section Item	Original	Amendment 3.1	Rationale
1.1. Schedule of Activities		**Mammogram at Week 52, Week 104/Early Termination, and Unscheduled** **X[dd]**	Added mammogram for patients who are ≥ 40 years of age.
1.1. Schedule of Activities Footnote r	~~This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within 4 weeks after completion of the Week 36 or Week 52 scan. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event.~~	**See Section 6.5.2.6 for details on the timing and follow-up of bone densitometry.**	Clarified bone densitometry follow-up.
1.1. Schedule of Activities Footnote s	Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed based on the timing of the Early Termination visit. ~~For Early Termination occurring after Week 24 and before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event, and follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. For Early Termination occurring after Week 36 and before Week 52, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2% or most recent DXA result was after Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. For Early Termination occurring between Week 52 and Week 104, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination, and follow-up DXA~~	Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed based on the timing of the Early Termination visit **(see Section 6.5.2.5)**.	

Section Item	Original	Amendment 3.1	Rationale
	~~is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline~~		
1.1. Schedule of Activities Footnote t	Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details)~~,~~ at Week 52 for all patients. ~~All~~ patients ~~are eligible for a biopsy at Week 104~~; however, patients will have the option to opt out.	Endometrial biopsies are to be done per instructions in the parent study. Procedures for handling and shipping biopsy samples to the central laboratory for analysis are described in the Investigator Site File. An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 only (see MVT-601-3101 protocol for details) **and** at Week 52 **and Early Termination visit** for all patients. **This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all** patients **who complete the open-label extension**; however, patients will have the option to opt out.	Added an endometrial biopsy at the Early Termination visit to assess endometrial safety in patients who were on study drug for more than 32 weeks. .
1.1. Schedule of Activities Footnote bb	Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and questioned about factors that may affect resumption of menses.	Patients whose menses have not resumed as of the Follow-up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted 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. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.**	Revised footnote to clarify procedures for when a patient is lost-follow-up.

Section Item	Original	Amendment 3.1	Rationale
1.1. Schedule of Activities Footnote dd		**For patients who are or will become ≥ 40 years old at the time of the Week 52 visit, Week 104 visit, or Early Termination visit only. See Section 6.5.2.9.**	Added clarification on timing of mammograms.
1.1. Schedule of Activities Footnote ee		**See Section 6.5.2.6, Section 6.5.2.7, and Section 6.5.2.8 to determine if additional follow-up is required.**	Add cross-references for additional information on safety follow-up.
3. Study Objectives and Endpoints		Objectives • **Overall pelvic pain, as measured by the NRS;** • **Analgesic use;** Endpoints • **Change from the parent Baseline in the mean NRS score;** • **Proportion of patients not using opioids;** • **Proportion of patients not using analgesics;**	Included additional objectives and corresponding endpoints to evaluate pelvic pain and analgesic use to align with analyses performed for the parent studies.
4.1. Overall Study Design	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, and bone mineral density with DXA.	Safety will be assessed throughout the study by the monitoring of adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECGs, **mammograms (for patients required to have this procedure; see Section 6.5.2.9), endometrial biopsies,** and bone mineral density with DXA.	. To assess patients' safety while on estradiol and norethindrone, a mammogram is added for patients who are 40 years of age or older.
4.1. Overall Study Design	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+ 0.5) months after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses.	Status of menstruation recovery will be documented at the Follow-up visit. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of menses. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to**	Clarified procedures for when a patient is lost to follow-up.

Section Item	Original	Amendment 3.1	Rationale
		contact the patient by telephone, a certified letter must be sent to the patient.	
4.5. Removal of Patients from Therapy		**Evidence of malignant breast lesion(s) or breast carcinoma on Week 52 or Week 104/Early Termination or most recent mammogram or additional breast imaging (see Section 6.5.2.9 for more information on mammogram at Week 52 or Week 104/Early Termination).**	Included removal criteria for findings resulting from mammogram.
4.6. Contraception /Pregnancy Avoidance	In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study including through 30 days following the last dose of study drug, unless any of the following apply:	**All patients should be counseled at every visit to adhere to the use of protocol allowed contraceptive methods.** In this study, medications and devices containing hormones for contraception are excluded, and patients must agree to use non-hormonal contraception throughout the study including through 30 days following the last dose of study drug, unless any of the following apply:	Added language for increased counselling on contraception.
4.7. Novel Coronavirus 2019 Guidance		**Guidance for conducting clinical trials during the novel coronavirus 2019 (COVID-19) pandemic is included in Appendix 9.**	Included COVID-19 pandemic guidance to ensure that the safety of patients is maintained, the study continues to be conducted in compliance with good clinical practice (GCP), and risks to the integrity of the study are minimized.
5.1. Treatments Administered Table 5-1	Description of MVT-601-~~3003~~ Study Drugs	Description of MVT-601-**3103** Study Drugs	Corrected study number.
5.10.1. Prohibited Medications Table 5-2	Intrauterine devices: levonorgestrel ~~copper~~	Intrauterine devices: levonorgestrel	Removed copper to reduce confusion with inclusion criterion 6c.
6. Study Assessments and Procedures	The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File.	The timing of each study assessment and procedure is provided in the Schedule of Activities (see Section 1.1). Study procedures are briefly described within Section 6.5. Further details of the procedures are provided in the Investigator Site File. **Guidelines to address**	Included COVID-19 pandemic guidance.

Section Item	Original	Amendment 3.1	Rationale
		the COVID-19 pandemic are included in Appendix 9.	
6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)	An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details), ~~at~~ Week 52 for all ~~subjects~~. ~~All patients will be eligible for the Week 104 biopsy~~; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78, and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.	An endometrial biopsy will have been performed at the parent study Week 24 visit for all patients who participated in MVT-601-3101 (see MVT-601-3101 protocol for details)**. An endometrial biopsy is required at** Week 52 **and the Early Termination visit** for all **patients**. **This procedure is not required at the Early Termination visit in patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the procedure may be done if it will aid in the evaluation of an ongoing adverse event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension**; however, patients will have the option to opt out. Safety monitoring for this study includes physical examination, clinical laboratory tests, pregnancy tests, and adverse event collection at each visit. Clinical chemistries will be collected at each visit. A complete blood count will be collected at Week 24/Baseline, Week 28, Week 36, Week 52, Week 65, Week 78**, Week 91,** and Week 104. At the Week 24/Baseline visit, Week 52 visit, and Week 104 visit, additional tests include fasting (at least 8 hours, other than water) glucose, lipid profile, and hemoglobin A1c.	Added endometrial biopsy at the Early Termination visit to assess endometrial safety on patients who were on study drug for more than 32 weeks.
6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)	Electrocardiograms will be performed at the Week 24/Baseline ~~and the~~ Week 52 visits.	Electrocardiograms will be performed at the Week 24/Baseline, Week 52, **and Week 104/Early Termination visits**.	Added Week 104/early termination visit ECG to align with Schedule of Activities.

Section Item	Original	Amendment 3.1	Rationale
6.2. Open-Label Treatment Period (Week 24/Baseline to Week 104)		**A mammogram will be performed at Week 52 or at Week 104/Early Termination for women who are or become ≥ 40 years old during the study (see Section** 6.5.2.9).	Added mammogram for patients who are ≥ 40 years of age.
6.3. Early Termination Visit and Follow-up Visit	All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. B~~one densitometry may be performed at the investigator's discretion, if it aids in follow-up of an ongoing adverse event(s)~~. Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.	All patients withdrawing from the study prior to Week 104 will complete an Early Termination visit. The Early Termination visit procedures are identical to those of Week 104. **An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse event.** Follow-up bone densitometry findings for patients who terminate from the study early will proceed according to the rules provided in Section 6.5.2.6.	Added an endometrial biopsy at the Early Termination visit to assess endometrial safety on patients who were on study drug for more than 32 weeks.
6.4. Unscheduled Visits	Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, 12-lead ECG, study drug compliance and dispensation, eDiary review, dispensation or prescription of protocol-specified analgesics, etc, may be conducted as	Unscheduled visits may be performed at any time during the study whenever necessary to assess for or follow-up on adverse events, at the patient's request, or as deemed necessary by the investigator. The date and reason for the Unscheduled visit should be recorded in the source documentation. The following activities should be completed at Unscheduled visits: recording of reason for the visit, concomitant medication review, and evaluation of adverse events. In addition, procedures such as vital signs, weight, complete physical examination, sign- and symptom-directed physical examination, clinical laboratory assessment, urinalysis, urine pregnancy testing, pharmacodynamic sampling, **mammogram (for patients required to have this procedure; see Section 6.5.2.9),** 12-lead ECG, study drug compliance and dispensation, eDiary review,	Added mammogram for patients who are ≥ 40 years of age.

Section Item	Original	Amendment 3.1	Rationale
	needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.	dispensation or prescription of protocol-specified analgesics, etc, may be conducted as needed. See the Schedule of Activities (Section 1.1) for tests that may be performed, as indicated at an Unscheduled visit. The investigator should consult with the medical monitor, if needed, to discuss Unscheduled visit testing. The investigator should obtain approval from the sponsor to perform an unscheduled endometrial biopsy or DXA, unless urgently indicated.	
6.5.2.4. Clinical Laboratory Tests		**For patients with incomplete recovery of bone mineral density loss at the 6- and 12-month post-treatment follow-up visit, clinical laboratory tests should be performed (see Section 6.5.2.6).**	Included clinical laboratory evaluations associated with bone densitometry follow-up.
6.5.2.4 Clinical Laboratory Samples		**These laboratory assessments will be submitted to the central laboratory. If these laboratory assessments are scheduled to occur after the study database is locked, they will be performed at a local laboratory.**	Added language to clarify procedure for laboratory assessment during study and post database lock.
6.5.2.6. Bone Mineral Density	Determination of bone mineral density by DXA at Early Termination and follow-up of findings will proceed according to the following rules: • ~~For Early Termination occurring between Week 24 and Week 52:~~ – For Early Termination occurring before Week 36, DXA is not required at Early Termination visit unless it will aid in the assessment of an adverse event.	Determination of bone mineral density by DXA at the Early Termination **visit or at the Week 104 visit** and follow-up of findings will proceed according to the following rules: **Early Termination and 6-Month Post-Treatment DXA** • **For patients who early terminate**: o For Early Termination occurring before Week 36, DXA is not required at the Early Termination visit	Clarified follow-up procedures for bone mineral density loss. Lowered threshold for post-treatment follow-up in order to assess the trajectory of BMD recovery in patients with a lesser degree of BMD loss. Added language to specify follow up procedure for bone mineral density loss at Week 104 visit.

Section Item	Original	Amendment 3.1	Rationale
	~~Follow-up DXA required at 6 months (± 1 month) if most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline.~~ – For Early Termination occurring after Week 36, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination. Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline. – Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline. ~~• For Early Termination occurring between Week 52 and Week 104:~~ ~~– DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination.~~	unless it will aid in the assessment of an adverse event **or if the most recent DXA bone mineral density loss at lumbar spine (L1-L4) or total hip was > 2% relative to the parent study baseline. In this case, follow-up DXA is required at 6 months (± 1 month).** • For Early Termination occurring **at or** after the Week 36 visit, DXA is required at Early Termination unless a DXA result is available from within six weeks prior to Early Termination. **Most recent DXA was at Week 24 visit:** Follow-up DXA is required at 6 months (± 1 month) if the most recent DXA scan was at Week 24 and bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 2%, relative to the parent study baseline; **Most recent DXA was after Week 24 visit:** Follow-up DXA is required at 6 months (± 1 month) if, on the most recent DXA scan in the open-label extension study, bone mineral density	

Section Item	Original	Amendment 3.1	Rationale
	~~Follow-up DXA is required at 6 months (± 1 month) if on the most recent DXA, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 7%, relative to parent study baseline.~~	loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline; **Study Completion and 6-Month Post-Treatment DXA** • **For patients who complete the open-label extension study:** **Follow-up DXA is required at 6 months (± 1 month) if, at the Week 104 visit or on the most recent DXA scan, bone mineral density loss at the lumbar spine (L1-L4) or total hip was > 3%, relative to the parent study baseline.** **Note: Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.** **Patients Who Have Previously Completed or Early Terminated from the Study** **Patients who have previously completed or early terminated from the study prior to Protocol Amendment 3.1 may not have undergone post-treatment DXA according to the current protocol requirements. To allow for further follow-up of these**	

Section Item	Original	Amendment 3.1	Rationale
		patients, it is strongly recommend that attempts be made to contact the patients who met the protocol specified threshold of > 3% bone loss at or after the Week 36 DXA scan to obtain a post-study follow-up DXA scan at 6 months (± 1 month) from last dose of study drug, if such a scan has not been scheduled or performed. For patients who are already out of this 6-month window, an unscheduled post-treatment follow-up DXA scan is recommended. **12-Month Post-Treatment DXA** • **If patients have 6-month post-treatment follow-up scans that show bone loss of > 1.5% at the lumbar spine and/or > 2.5% at total hip compared with the parent study baseline, patients are strongly encouraged return to the clinic for an additional post-treatment follow-up scan 12 months from the date of the last dose of the study drug. Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.** • **If patients have 12-month post-treatment follow-up scans that show bone loss of ≥ 3% at the**	

Section Item	Original	Amendment 3.1	Rationale
		lumbar spine and/or total hip compared with the parent study baseline, patients are recommended to be referred to and strongly encouraged to see a bone specialist for further evaluation of the bone loss. • **Note 1: Patients undergoing 6-month post-treatment follow-up should also have the following clinical laboratory evaluations: vitamin D, thyroid-stimulating hormone, parathyroid hormone, creatinine, calcium, and phosphorous.** **Note 2: When a patient is referred to a bone specialist for evaluation and management, Myovant will provide a Bone Consultation Letter to the investigator for this additional bone consult and will request the site to provide a summary of the evaluation and management plan after the consultations is complete.**	
6.5.2.7. Endometrial Biopsy	Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at Week 52 for all patients. ~~At Week 104, all patients will be eligible for an additional endometrial biopsy~~; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not ~~preclude entry into the study or~~ indicate withdrawal from the study. The Week 52 ~~and~~ Week 104 endometrial biopsy samples will be submitted to the central	Additional assessment of the effects of relugolix co-administered with low-dose estradiol and norethindrone acetate on the endometrium will be performed at the Week 52 **and Early Termination visit** for all patients. **An endometrial biopsy is required for all patients at the Early Termination visit except for patients whose last dose of study drug was taken during Week 32 or earlier or within four weeks after completion of the Week 52 endometrial biopsy. However, the endometrial biopsy may be obtained if it will aid in the evaluation of an ongoing adverse**	Clarified endometrial biopsy timing. Add endometrial biopsy at the Early Termination visit to assess endometrial safety on patients who were on study drug for more than 32 weeks. Erroneous phrase has been deleted.

Section Item	Original	Amendment 3.1	Rationale
	laboratory. If the Week 52~~ or~~ Week 104 biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:	**event. An endometrial biopsy at Week 104 is recommended for all patients who complete the open-label extension**; however, patients will have the option to opt out. Patient participation in the Week 104 endometrial biopsy is voluntary and refusal to participate will not preclude entry into the study or indicate withdrawal from the study. The Week 52**,** Week 104**, and Early Termination** endometrial biopsy samples will be submitted to the central laboratory. If the Week 52**,** Week 104**, or Early Termination** biopsy specimen is inadequate, a transvaginal ultrasound for endometrial thickness should be obtained and read locally. The transvaginal ultrasound findings will be used to determine if further action is required:	
6.5.2.7. Endometrial Biopsy	Patients who have endometrial hyperplasia or endometrial carcinoma will be withdrawn from study drug treatment and followed per instructions in the parent study protocol.	Patients who have endometrial hyperplasia or endometrial carcinoma will be withdrawn from study drug treatment and followed per instructions in the parent **and/or extension** study protocol. **Investigators should contact the medical monitor if a patient refuses to have an endometrial biopsy at Week 52 or the Early Termination visit.**	Changed to reflect existing text in Section 4.5. Clarified investigator role in communicating to sponsor when a patient refuses the endometrial biopsy.
6.5.2.8. Status of Menstruation Recovery	If the first menstruation after the end of study treatment administration is observed before the Follow-up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted ~~again~~ by telephone 3 (+0.5) months after the Follow-Up visit to determine if menses has resumed and will	If the first menstruation after the end of study treatment administration is observed before the Follow-Up visit, the date of onset of the first menstruation is recorded in the eCRF. Patients whose menses has not resumed as of the Follow-Up visit for whom there is no explanation for the lack of resumption (eg, medical procedure or medications) will be contacted by telephone 3 months (+ 0.5 months) after the Follow-Up visit to determine if menses has resumed and will be asked about factors that may affect resumption of	Clarified procedures for when a patient is potentially lost to follow-up.

Section Item	Original	Amendment 3.1	Rationale
	be asked about factors that may affect resumption of menses.	menses. **If a patient is lost to follow-up, three documented attempts should be made to contact the patient by telephone. If unable to contact the patient by telephone, a certified letter must be sent to the patient.**	
6.5.2.9. Mammogram		**A mammogram will be performed at the Week 52 or Week 104/Early Termination visit (see the Schedule of Activities in Section 1.1) for patients ≥ 40 years of age at the time of the visit. If a patient had a recent mammogram per standard of care within the 6 months before Week 52 that was Breast Imaging Reporting and Data System category 1 or 2 or equivalent or had benign findings, as determined by the investigator or medical monitor, a mammogram is not required at Week 52 but should be completed by Week 104/Early Termination. If a patient turns 40 years old after the Week 52 visit has occurred, a mammogram should be performed no later than the Week 104/Early Termination visit. All mammogram results will be read locally using Breast Imaging Reporting and Data System categories or equivalent (see Appendix 8) and recorded in the eCRF. The following actions will be taken depending on the reading:** • **Category 1 or 2 or equivalent: normal mammogram; no further action is required unless determined by the investigator or medical monitor;** • **Category 0 or 3 or equivalent: adjunctive breast imaging or follow-up mammogram will be required, and the investigator should contact the medical monitor for approval of additional breast imaging;**	To assess patients' safety while on estradiol and norethindrone, a mammogram is added for patients ≥40 years of age and actions to be taken for mammogram findings are specified.

Section Item	Original	Amendment 3.1	Rationale
		• **Category 4 to 6 or equivalent: the investigator should contact the medical monitor within 24 hours.** • **Patients who have malignant breast lesion(s) or breast carcinoma will be withdrawn from study drug treatment (see Section 4.5).**	
7.2.1. Adverse Event Reporting Period	Adverse events and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor ~~if the investigator assesses the event as related to the study drug treatment~~.	Adverse events and serious adverse events will be collected under this extension study protocol from the administration of the first dose of extension study drug until the Follow-up visit approximately 30 days after the last dose of study drug or the date of initiation of another investigational agent or hormonal therapy affecting the hypothalamic-pituitary-gonadal axis or surgical intervention for endometriosis, whichever occurs first, as also specified in the study Schedule of Activities (Section 1.1). Serious adverse events reported to the investigator after the safety reporting period should be reported to the sponsor **regardless of causal relationship to study drug treatment**.	Clarified reporting instructions.
7.6 Serious Adverse Event Reporting	The contact information for submission of serious adverse events, adverse events of clinical interest (defined in Section **Error! Reference source not found.**), and events of overdose is available on the ~~Serious Adverse Event report form~~ and is as follows:	The contact information for submission of serious adverse events, adverse events of clinical interest (defined in Section **Error! Reference source not found.**), and events of overdose is available on the **Safety Report Form** and is as follows:	Corrected name of form.
7.7. Study Drug Overdose Management	Contact the medical monitor ~~immediately~~;	Contact the medical monitor **within 24 hours**;	Clarified timing of overdose reporting requirements.
7.8. Pregnancy Reporting	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	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	Added clarification about the documentation of pregnancy.

Section Item	Original	Amendment 3.1	Rationale
	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 form, as available.	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 form, as available. **Document the pregnancy in the eCRF as well.**	
Section 7.10 Table 7-2 Risk of Estradiol (1.0 mg)/ Norethindrone Acetate (0.5 mg)	Monitoring and Withdrawal Criteria Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each visit.	Monitoring and Withdrawal Criteria Clinical chemistries assessing liver tests, fasting glucose and lipids, and urine pregnancy tests will be performed throughout the study. Adverse events will be recorded at each **study** visit**;** **A mammogram will be performed at Week 52 or at the Week 104/Early Termination for women who are or become ≥ 40 years old during the study, with specified discontinuation criteria. Adverse events will be recorded**.	Added details to correspond with the addition of mammograms.
9. Statistical Considerations and Data Analyses		**The study may be closed pending selected contingent safety procedures conducted after the last patient's Week 104/Early Termination or Follow-Up visit. After the study is closed, any pending required follow-up testing of bone mineral density and endometrial biopsies or for menstruation recovery beyond the Follow-Up visit will be captured and reported.**	Added language to provide guidance on site closure and pending follow up procedures
9.2. Analysis Population	Efficacy data analyses will be performed on the ~~Modified Intent-to-Treat (mITT) Population,~~ defined as all patients who were randomized in a parent study ~~(MVT-601-3101 or MVT-601-3102)~~ and who have received any amount of randomized study drug.	Efficacy data analyses will be performed on **the Extension Study Population,** defined as all patients who enrolled into **MVT-601-3103 and** who have received any amount of randomized open-label study drug **in MVT-601-3103.**	To clarify the analysis populations for efficacy and safety data of the extension study.

Section Item	Original	Amendment 3.1	Rationale
	Safety data analyses will be performed on the Safety Population, defined as all ~~patients who were randomized in a parent study and~~ who have received any amount of ~~randomized~~ study drug.	Safety data analyses will be performed on the Safety Population, defined as all **enrolled patients** who have received any amount of **study MVT-601-3103** study drug.	
9.4. Efficacy Analyses	Unless otherwise specified, efficacy analyses will be conducted using the ~~mITT~~ Population.	Unless otherwise specified, efficacy analyses will be conducted using the **Extension Study** Population. • **Change from the parent Baseline in the mean NRS score;** • **Proportion of patients not using opioids;** • **Proportion of patients not using analgesics;**	Included additional endpoints to evaluate pelvic pain and analgesic use to align with analyses performed for the parent studies.
9.5 Safety Analyses	Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, ~~and~~ bone mineral density with DXA. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.	Safety assessments will include treatment-emergent adverse events, vital signs and weight, physical examinations, clinical laboratory tests, 12-lead ECG, bone mineral density with DXA**, mammograms (for patients required to have this procedure; see Section 6.5.2.9), and endometrial biopsy**. Safety summaries by treatment group will be performed using treatment groups defined based on the actual randomized treatment received in the parent study.	Included added assessments.
Appendix 8 Breast Imaging Reporting and Data System		Added appendix.	Corresponding information for the addition of mammograms.
Appendix 9 Guidance for Study Conduct during the		Added appendix.	Details regarding the conduct of the study during the COVID-19 pandemic.

Section Item	Original	Amendment 3.1	Rationale
COVID-19 Pandemic			