1.0 Title Page

Clinical Study Protocol M16-383

A Study to Evaluate Safety and Efficacy of Elagolix Alone or Elagolix with Hormonal Add-Back in Subjects with Endometriosis with Associated Moderate to Severe Pain

AbbVie Investigational Product:	Elagolix
Date:	29 September 2017
Development Phase:	3
Study Design:	The study employs an open label 3 month run in period with a 21 month randomized, double-blind active treatment period.
Investigator(s):	Multicenter Trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted]

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information
No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Synopsis

AbbVie Inc.	**Protocol Number:** M16-383
Name of Study Drug: Elagolix	**Phase of Development:** 3
Name of Active Ingredient: Elagolix sodium	**Date of Protocol Synopsis:** 29 September 2017
Protocol Title: A Study to Evaluate Safety and Efficacy of Elagolix Alone or Elagolix with Hormonal Add-Back in Subjects with Endometriosis with Associated Moderate to Severe Pain	
Objectives: The objectives of this study are to: • Compare the efficacy at Treatment Month 6 of dose escalation to elagolix 200 mg BID + estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA 1 mg/0.5 mg) QD versus continuing elagolix 150 mg QD in subjects who are incomplete efficacy responders to elagolix 150 mg QD at Treatment Month 3 • Assess the effects of elagolix 150 mg QD and elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD on BMD after up to 24 months of treatment • Evaluate the modifiable and non-modifiable risk factors associated with changes in Bone Mineral Density (BMD) over 24 months of treatment	
Investigators: Multi-center; Investigator information is on file at AbbVie.	
Study Site(s): Approximately 200	
Study Population: Premenopausal females (aged 18 – 49 years, inclusive) who have a documented surgical diagnosis of endometriosis (e.g., laparoscopy or laparotomy) established by visualization or histology within 10 years prior to entry into Washout or Screening and with moderate to severe pain.	
Number of Subjects to be Enrolled: Approximately 890	
Methodology: This is a Phase 3, dose-escalation study designed to evaluate the safety and efficacy of both elagolix 150 mg QD and elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD over 24 months in the management of endometriosis with associated moderate to severe pain in premenopausal women. After establishing eligibility, the study starts with open-label treatment on elagolix 150 mg QD for the first 3 months. Following the Treatment Month 3 visit and continuing through Treatment Month 24, the study is conducted in a double-blinded manner with treatment assignment determined based on the efficacy responder status assessed at Months 3 and 6.	

Methodology (Continued):

At the Treatment Month 3 study visit, the efficacy responder status of each subject will be determined based on the responses to the Daily Diary endometriosis-associated pain score via a Numeric Rating Scale (NRS) in the electronic diary (e-Diary). The results of the responder status determination are blinded and the details of the responder status calculation are outlined below. Subjects determined to be efficacy responders at the Treatment Month 3 visit will continue to dose with elagolix 150 mg QD in a blinded manner throughout the remainder of the 24-month Treatment Period. Subjects determined to be incomplete efficacy responders at the Treatment Month 3 visit will be randomized in a 1:1 ratio to receive elagolix 150 mg QD or elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD. Subjects who were randomized to receive elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD will continue with this treatment in a blinded manner throughout the remainder of the 24-month Treatment Period.

At the Treatment Month 6 study visit, the efficacy responder status of each subject will be determined in the same blinded manner as at the Treatment Month 3 study visit. Subjects who randomized at Treatment Month 3 to receive elagolix 150 mg QD and are subsequently determined to be efficacy responders at Treatment Month 6 will continue to receive elagolix 150 mg QD throughout the remainder of the 24-month Treatment Period. Subjects who randomized at Treatment Month 3 to receive elagolix 150 mg QD and are subsequently determined to be incomplete efficacy responders at Month 6 will receive elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD throughout the remainder of the 24-month Treatment Period.

The Treatment Groups are described below:

Day 1 Through Month 3 (Open-Label):

- Open-Label elagolix 150 mg QD

Month 4 Visit Through Month 6 (Double-Blind):

- **(A)** Efficacy responders to elagolix 150 mg QD at Month 3
- **(B)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3 and randomized to elagolix 150 mg QD treatment group
- **(C)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3 and randomized to elagolix 200 mg BID plus E2/NETA 1/0.5 mg QD treatment group

Month 7 Through Month 24 (Double-Blind):

- **(A)** Efficacy responders to elagolix 150 mg QD at Month 3 and continue treatment through Month 24
- **(C)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3 and randomized to elagolix 200 mg BID plus E2/NETA 1/0.5 mg QD treatment group and continue treatment through Month 24.
- **(D)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 150 mg QD treatment group and remain incomplete efficacy responders at Month 6, dose increased to elagolix 200 mg BID plus E2/NETA 1/0.5 mg QD through Month 24
- **(E)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 150 mg QD treatment group and are efficacy responders at Month 6 continue treatment through Month 24

Study Duration:

The total duration for this study is approximately 27 to 50 months, consisting of 4 study periods:

- Washout Period – up to 10 months prior to Screening (only applicable if subject is taking exclusionary medication at the time of consenting; duration of washout depends on the type of excluded medication being taken)
- Screening Period – approximately 1.5 to 4 months prior to the first dose of study drug.
- Treatment Period – up to a total of 24-months treatment duration consisting of the following:
  - Open-Label Run-In Period: 3 month treatment duration from Day 1 to Treatment Month 3 study visit
  - Double-Blind Active Treatment Period: Treatment Month 3 study visit through Treatment Month 24 study visit
- Follow-up Period – up to 12 months following the last dose of study drug

Washout Period:

Following informed consent, subjects who have been taking exclusionary medications prior to screening that require discontinuation (washout), must enter the Washout Period. The duration of the required washout period is based on the excluded medication being taken. Applicable study procedures may be performed, such as medical, social and gynecological history (including documentation of diagnosis of endometriosis via surgical visualization, histological diagnosis), a brief physical examination with vital signs and urine pregnancy testing; protocol-related adverse event review and documentation of current medications.

Subjects must complete the Washout Period and have had at least 1 menstrual period (menses) prior to entering the Screening Period. Subjects will also begin the use of non-hormonal dual contraception during the Washout Period and receive counseling on the importance of consistent, appropriate and effective use of contraception, and contraceptives dispensed, as necessary.

Screening Period:

Following informed consent (if Washout was not required), subjects will enter into the Screening Period. Eligible subjects will have documentation of a surgical confirmation of endometriosis. In addition to medical and gynecological history, specific history will be obtained to help identify potential risk factors/predictors related to changes in BMD, including modifiable and non-modifiable risk factors. The following safety assessments will be completed during the Screening Period: a dual energy x-ray absorptiometry (DXA) of the lumbar spine, total hip and femoral neck to document baseline BMD; a transvaginal ultrasound (TVU) to rule out any clinically significant gynecological disorders such as ovarian cysts, fibroids or endometrial polyps; a Papanicolau (Pap) test to rule out malignancy or pre-malignant changes; a mammogram in subjects 39 years of age or older if one has not been performed within 3 months prior to start of Screening; baseline ECG; as well as clinical laboratory testing.

Screening Period (Continued):

An electronic diary (e-Diary) will be provided to subjects to begin recording dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) via the 4 point Endometriosis Daily Pain Impact Diary; Daily Diary endometriosis-associated pain score via NRS; dyspareunia (if applicable) via a 4-point scale and the presence and intensity of uterine bleeding. Subjects will record use of protocol allowed analgesic rescue medications for endometriosis-associated pain in the e-Diary. A minimum of 45 days of daily e-Diary entries are required to be completed during the Screening Period. To be considered eligible for the study, during the last 35 calendar days of the Screening Period, subjects must have at least 2 days of moderate or severe DYS and one of the following: at least 2 days of moderate or severe NMPP with an average NMPP score of at least 1.0, OR at least 4 days of moderate or severe NMPP and an average NMPP score of at least 0.5. Additionally, subjects must have 2 menstrual cycles with cycle lengths of 21 – 38 days, and at least 1 full menstrual cycle (i.e., 2 menses or menstrual periods) must be documented in the e-Diary during the Screening Period. Subjects will be allowed to take protocol-specified analgesic rescue medication for endometriosis-associated pain and will record use daily in the e-Diary. Protocol specific analgesic rescue medication for endometriosis-associated pain will include four equivalent NSAID choices and two equivalent opioid choices); use of other rescue analgesic or the use of prophylactic analgesic medications for endometriosis-associated pain is not allowed. The subject and Investigator will decide on the appropriate rescue analgesic medications for that subject (based on the approved options).

Subjects are also required to use appropriate non-hormonal methods of contraception (as applicable). Contraceptive counseling will be provided and contraceptives dispensed, as necessary.

Treatment Period:

The Treatment Period begins with Study Day 1. Study Day 1 will occur between Cycle Days 1 to 10 of a subject's menses (Cycle Day 1 is defined as first day with full menstrual flow) for all subjects who meet eligibility criteria during the Screening Period. On Study Day 1, all subjects will begin open-label dosing with elagolix 150 mg QD. The first dose of study drug will be administered at the study site on Day 1 and study drug kits will be dispensed to subjects to continue daily dosing. Monthly on-site study visits will be conducted during the first 6 months of the Treatment Period. Subjects will be expected to come in to the site every other month during Treatment Months 7 – 12 and every third month during Treatment Months 13 – 24. Telephone contacts will be conducted at months without an on-site visit. Subjects will be asked to complete various patient-reported outcome (PRO) questionnaires at designated study visits. At the Day 1 visit (prior to dosing) and at all monthly visits (on-site and telephone contacts), site staff will administer to subjects the overall endometriosis-associated pain questionnaire, an 11-point NRS with a 7-day recall period. Starting at Treatment Month 1 and at all on-site visits thereafter, subjects will complete the Patient Global Impression of Change (PGIC) questionnaire. Pregnancy (serum and/or urine) tests will be performed at each visit throughout the Treatment Period. Urine pregnancy test kits will be provided to subjects for use at home for the study visits when subjects are not required to come into the clinic/site. Subjects will self-administer the tests and report the results to the site at the telephone contact visits. A positive urine pregnancy test result must be confirmed with a serum pregnancy test. If a serum pregnancy test result is positive at any time during the Treatment Period, study drug will be discontinued.

Treatment Period (Continued):

Subjects will continue to use the daily e-Diary to record DYS, NMPP; dyspareunia; Daily Diary endometriosis-associated pain score via NRS; rescue analgesic use for endometriosis-associated pain and the presence and intensity of uterine bleeding through Treatment Month 6. Throughout the 24-month Treatment Period, all subjects will be allowed to take protocol specified analgesic medication for endometriosis-associated pain. Use of non-protocol specific analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed. After Treatment Month 6 use of protocol specific analgesic rescue medications will be assessed and documented at the study visits.

At designated study visits during the 24-month Treatment Period, blood samples will be collected for clinical safety labs, including vitamin D levels. In addition, blood samples will be collected for assay of serum estradiol, plasma concentrations of elagolix and norethindrone.

BMD will be assessed throughout the Treatment Period. Following baseline, DXA scans will be obtained at Treatment Months 6, 12, 18 and 24. A DXA scan will be required if a subject discontinues at the time of or after the Treatment Month 6 visit or if the reason for premature discontinuation is due to the occurrence of a fracture or any newly diagnosed bone condition.

Vital signs assessments will be conducted at all on-site study visits. Additional safety assessments are completed as appropriate at designated study visits throughout the Treatment Period. Adverse event and concomitant medication review will be conducted at all study visits.

Criteria for Assessment of Subject Status Following the Open-Label Run-In Period:

At the Treatment Month 3 study visit, subjects will be assessed as either an 'efficacy responder' or an 'incomplete efficacy responder' based on responses entered in the e-Diary on the Daily Diary endometriosis-associated pain score via NRS. The status of a subject will be determined (in a blinded manner) within the e-Diary system as follows:

- Efficacy responder: $\geq$ 30% decrease (improvement) from Baseline based on the average of the daily Diary endometriosis-associated pain score via NRS over a 35 day window
- Incomplete efficacy responder: < 30% decrease (improvement) from Baseline based on the average of the Daily Diary endometriosis-associated pain score via NRS over a 35 day window

Following conclusion of the Open-Label Run-In Period, treatment arm assignment for all subjects will become and remain blinded for the remainder of the 24-month Treatment Period.

Dose Escalation During the Treatment Period:

Subjects assessed as "efficacy responders" (as defined above) at Treatment Month 3 visit will be assigned to continue dosing with elagolix 150 mg QD (Group A) in a blinded manner via Interactive Response Technology (IRT). All other subjects assessed as "incomplete efficacy responders" at Treatment Month 3 visit will be assigned randomly (in an equal ratio) via IRT to either elagolix 150 mg QD (Group B) or elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (Group C) for 3 months. To preserve the blind, IRT will be utilized for study drug assignment for all subjects. The first dose from the newly assigned study drug kit at Treatment Month 3 will be administered at the site. The pharmacokinetic and pharmacodynamics samples must be obtained prior to study drug administration at the Treatment Month 3 visit.

Dose Escalation During the Treatment Period (Continued):

At the Treatment Month 6 study visit, in a blinded manner via IRT, all subjects who were incomplete efficacy responders and randomly assigned at Treatment Month 3 to elagolix 150 mg QD will again be assessed for efficacy response in the same manner as was done at the Treatment Month 3 visit. All subjects in this group (Group B) who become efficacy responders will continue dosing with elagolix 150 mg QD in a blinded manner (Group E). All other subjects in this group who are assessed as incomplete efficacy responders at Treatment Month 6 will escalate dosing to elagolix 200 mg BID plus E2/NETA
(1 mg/0.5 mg) QD (Group D). To preserve the blind, IRT will be utilized for treatment assignment of all subjects; however, only subjects randomly assigned at Treatment Month 3 to the elagolix 150 mg QD (Group B) will have a chance for dose modification. The first dose from the newly assigned study drug kit at Treatment Month 6 will be administered at the site. The pharmacokinetic and pharmacodynamics samples must be obtained prior to study drug administration at the Treatment Month 6 visit.

The treatment assignments following the Treatment Month 6 study visit will continue for all subjects for the duration of the 24-month Treatment Period in a blinded manner. There will not be further dose adjustments following the Treatment Month 6 visit for any subject.

BMD Assessment and Subject Specific Safety Stopping Criteria for BMD During the Treatment Period:

DXA scans of the lumbar spine, total hip and femoral neck will be obtained at Treatment Months 6, 12, 18 and 24. If the results of any post-baseline DXA prior to the Treatment Month 24 timepoint, as read by the central imaging vendor selected for the study, document a Z-score (for subjects < 40 years of age at the time of the Screening DXA) or a T-score (for subjects ≥ 40 years of age at the time of the Screening DXA) of < –2.5 in the lumbar spine, total hip or femoral neck, or > 8% decrease in BMD from baseline the subject must be discontinued from study drug dosing and will enter the Follow-Up Period.

Follow-Up Period:

Subjects will enter the Follow-Up Period for up to 12 months to assess bone recovery after up to 24 months of treatment with the study drug. Subjects who prematurely discontinue (PD) from the study at the time of or after the Treatment Month 6 visit or if the reason for PD is related to bone fracture will enter the Follow-Up Period.

DXA scans of the lumbar spine, total hip and femoral neck will be obtained. Any ongoing adverse events or adverse events of bone fracture, clinically significant BMD decrease or a newly diagnosed medically-related bone condition will be collected during the Follow-Up Period. Concomitant medication use will be reviewed at on-site visits.

The Follow-Up Period for the study should conclude for all subjects approximately 30 days after the last completed Treatment Month 24 visit.

Central Laboratory and Central Imaging Vendors:

DXA, TVU, safety clinical lab samples will be analyzed/evaluated using central laboratories or imaging vendors. Assays for pharmacokinetics and pharmacodynamics will be analyzed at AbbVie.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- Subject is a premenopausal female 18 to 49 years of age (inclusive) at the time of Screening.
- Subject has a documented surgical diagnosis (e.g., laparoscopy or laparotomy) of endometriosis established by visualization or histology within 10 years prior to entry into Washout or Screening,
- Subject must agree to use only those rescue analgesics permitted by the protocol during the Screening and Treatment Periods for her endometriosis-associated pain.
- Subject must have the following documented in the e-Diary during the last 35 days prior to Study Day 1:
  - At least 2 days of "moderate" or "severe" DYS, AND either,
  - At least 2 days of "moderate" or "severe" NMPP and an average NMPP score of at least 1.0,

    OR
  - At least 4 days of "moderate" or "severe" NMPP and an average NMPP score of at least 0.5.

Main Exclusion:

- Subject has chronic pelvic pain that is not caused by endometriosis (e.g., interstitial cystitis, adenomyosis [as a dominant condition diagnosed by MRI or ultrasound], fibroids, pelvic inflammatory disease [PID], non-endometriosis-related pelvic adhesive disease, irritable bowel syndrome [IBS]), that requires chronic analgesic therapy, which would interfere with the assessment of endometriosis-associated pain.
- Subject is using any systemic corticosteroids for over 14 days within 3 months prior to Screening or is likely to require treatment with systemic corticosteroids during the course of the study. Over-the-counter and prescription topical, inhaled or intranasal corticosteroids are allowed.
- Subject has a history of any of the following:
  - Major depression or post-traumatic stress disorder (PTSD) within 2 years prior to the Screening Visit
  - Other major psychiatric disorder at any time (e.g., schizophrenia, bipolar disorder)
- Subject has a history of suicide attempts or answered "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening or prior to study drug dosing on Day 1.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

- Subject has any condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, spinal hardware, severe scoliosis or weight) or any history of osteoporosis or other metabolic bone disease or including:
  - Intercurrent bone disease (e.g., ostemalacia, osteogenesis imperfecta)
  - History or presence of an unstable condition that is associated with a decrease in BMD (e.g., uncontrolled hyperthyroidism, uncontrolled hyperparathyroidism, anorexia nervosa)
  - History of low-trauma hip or vertebral fractures (e.g., fracture resulting from a fall from a standing height or lower)
  - Bilateral hip replacement
  - Clinically significant hypocalcemia, hypo- or hyperphosphatemia, including during Screening (lab results)
  - Treatment with medication (excluding calcium and Vitamin D) for bone disease associated with a decrease in BMD.
- Screening DXA results of the lumbar spine (L1 – L4), femoral neck or total hip BMD corresponding to less than 2 or more standard deviations below normal (Z-score < –2.0 for subjects < 40 years of age, T-score for subjects ≥ 40 years of age).
- Subject has either
  - a newly diagnosed, clinically significant medical condition that requires therapeutic intervention (e.g., new onset hypertension) that has not been stabilized 30 days prior to enrollment on Day 1 OR
  - a clinically significant medical condition that is anticipated to required intervention during the course of study participation (e.g., anticipated major elective surgery) OR
  - an unstable medical condition that makes the subject an unsuitable candidate for the study in the opinion of the Investigator, (including, but not limited to, uncontrolled diabetes mellitus, uncontrolled hypertension, epilepsy requiring anti-epileptic medication, unstable angina, confirmed inflammatory bowel disease, hyperprolactinemia, clinically significant infection or injury).
- Subject has any conditions contraindicated with use of E2/NETA such as:
  - Current or history of deep vein thrombosis (DVT) or pulmonary embolism
  - Current or history (within 1 year of Screening) of arterial thromboembolic disease (e.g., stroke, myocardial infarction).

Investigational Product(s):	Elagolix 150 mg and 200 mg Estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA)
Dose(s):	Elagolix 150 mg QD Elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD
Reference Therapy:	Placebo to match elagolix; placebo to match E2/NETA
Mode of Administration:	Oral
Duration of Treatment:	Up to 24 months of treatment
Duration of Follow-Up:	Up to 12 months

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variables:

The co-primary efficacy endpoints will be the proportion of responders (treatment Group B versus treatment Group C) Month 6 based upon the mutually-exclusive scales for daily assessment of DYS and NMPP measured by the 4-point Endometriosis Daily Pain Impact Diary. Use of protocol specific analgesic medication for endometriosis-associated pain collected in the daily e-Diary will also be included in the responder definition.

Other Efficacy Endpoints:

The following efficacy variables will be collected in the daily e-Diary through Treatment Month 6 and will be summarized:

- DYS
- NMPP
- Dyspareunia
- Daily Diary endometriosis-associated pain score via Numeric Rating Scale (NRS)
- Rescue analgesic medication use

In addition, the following efficacy variables will be collected and summarized:

- PGIC
- Overall endometriosis-associated pain via NRS (7-day recall)
- Patient reported outcome (PRO) and Outcomes Rating Scales questionnaires

Safety:

BMD Assessments:

BMD assessments will be summarized. Modifiable and non-modifiable risk factors will be assessed as they relate to baseline BMD and changes in BMD over time, including: smoking and alcohol use, previous use of calcium and vitamin D, prior medications, race, age, height and weight (BMI), physical activity (collected via the International Physical Activity Questionnaire [August 2002] Short Last 7 days Self-Administered format) family history of fracture and family history of osteoporosis.

Other Safety Assessments:

Safety evaluations will include physical examinations, AEs and concomitant medications, clinical laboratory tests and vital sign measurements. Endometrial health will be assessed via TVU and biopsy.

Statistical Methods:

Efficacy:

The primary efficacy comparisons will be at Treatment Month 6 between the elagolix 200 mg BID plus E2/NETA treatment group (Group C) and elagolix 150 mg QD group (treatment Group B) in patients who are incomplete efficacy responders to elagolix 150 mg QD treatment at Month 3. Change and percent change from baseline in pain parameters collected via the e-Diary, proportion of responders for each pain parameter, change and percent change from baseline in protocol-specified rescue analgesic use, and other PROs will be summarized by month.

Statistical Methods (Continued):

Pharmacokinetic:

Plasma concentrations of elagolix and norethindrone will be listed for each subject by visit. Elagolix and norethindrone exposures will be summarized. Elagolix pharmacokinetic data may be combined with data from other studies to conduct population pharmacokinetic analysis and may be used in exposure-response analysis.

Pharmacodynamic:

Concentrations of estradiol will be obtained at designated visits throughout the study. Additional pharmacodynamic parameters may be calculated if useful in the interpretation of the data. Estradiol data may be combined with data from other studies and may be used for exposure-response analysis.

Safety:

All enrolled subjects who took at least one dose of the study drug will be included in the safety analyses.

Data collected during the 3 month Open-Label Period will be summarized for all subjects combined.

Baseline for all subjects will refer to the data obtained prior to dosing on Day 1 of the Open-label Run-in Period. In general, for continuous variables, descriptive statistics (mean, standard deviation, median, minimum and maximum) will be summarized by treatment group. Categorical data will be summarized with frequencies and percentages by treatment group. Unless otherwise specified, no statistical tests will be performed.

Analysis details will be specified in the SAP.

1.2 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
ABT	AbbVie
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice daily
BMD	Bone Mineral Density
CIN	Cervical Intraepithelial Neoplasia
CR	Controlled release
CYP3A	Cytochrome P450 3A
DYS	Dysmenorrhea
DXA	Dual Energy X-Ray Absorptiometry
E2	Estradiol
E2/NETA	Estradiol/Norethindrone acetate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e-Diary	Electronic Daily Diary
EHP-30	Endometriosis Health Profile-30
ePRO	Electronic Patient Reported Outcome
EQ-5D-5L	EuroQol-5D 5 Level
ER	Extended release
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin releasing hormone
HAV-IgM	Hepatitis A Virus immunoglobulin M
HBsAg	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C Virus Antibody
HCRU	Health Care Resource Utilization
HDL	High-density lipoprotein

HIV	Human Immunodeficiency Virus
HIV Ab	Human Immunodeficiency Virus Antibody
HPV	Human Papillomavirus
HSIL	High-Grade Squamous Intraepithelial Lesion
ICH	International Conference on Harmonization
ICF	Informed consent form
IEC	Independent Ethics Committee
IPAQ	International Physical Activity Questionnaire
IR	Immediate release
IRB	Institutional Review Board
IUD	Intrauterine device
IRT	Interactive Response Technology
LDL	Low-density lipoprotein
NMPP	Non-menstrual pelvic pain
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
Pap	Papanicolau
PD	Premature Discontinuation
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
PRO	Patient Reported Outcome
QD	Once a day
RBC	Red Blood Cell
SAE	Serious adverse event
SIS	Saline infusion sonography
TA MD	Therapeutic Area Medical Director
TSH	Thyroid Stimulating Hormone
TVU	Transvaginal Ultrasound
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire – Specific Health Problem

Pharmacokinetic and Statistical Abbreviations

ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AUC	Area under the plasma concentration-time curve
LOCF	Last Observation Carried Forward
MMRM	Mixed-model with repeated measures
ROC	Receiver Operating Characteristics
SAP	Statistical Analysis Plan
T_{max}	Time to maximum observed plasma concentration

Definition of Terms

Open Label Period	Portion of the Treatment Period (from Day 1 through Treatment Period Month 3) wherein all subjects will dose with unblinded active study drug (150 mg Elagolix QD).
Randomization	Blinded treatment arm assignment at the Treatment Period Month 3 visit based on responder status determination.
Re-assignment	Re-assignment at Treatment Period Month 6 of the incomplete efficacy responding subjects previously randomized to 150 mg elagolix alone.
E2/NETA	Estradiol (E2) 1 mg/norethindrone acetate (NETA) 0.5 mg
Month	A month is defined as 28 days.
Efficacy Responder	≥ 30% decrease (improvement) from baseline in the average score on the Daily Diary endometriosis-associated pain score via NRS for endometriosis-associated pain based on a 35 day window
Efficacy Incomplete Responder	< 30% decrease (improvement) from baseline in the average score on the Daily Diary endometriosis-associated pain score via NRS for endometriosis-associated pain based on a 35 day window

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3.0 Introduction

3.1 Endometriosis

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus.[1] Endometriosis primarily affects women of childbearing age, and is a frequently debilitating condition that is associated with a range of symptoms, the most common of which are dysmenorrhea (DYS) or painful menses, and non-menstrual pelvic pain (NMPP), as well as painful sexual intercourse or dyspareunia. Endometriosis is also a common reason cited for infertility.

The treatment of pain in women with endometriosis is remarkable for the number of therapeutic classes that are used to manage these symptoms and their use has been detailed in key clinical practice guidelines from the American College of Obstetricians and Gynecologists (ACOG),[2] American Society for Reproductive Medicine (ASRM),[3] European Society of Human Reproduction and Embryology (ESHRE),[4] the Society of Obstetrics and Gynecology Canada (SOGC) and the World Endometriosis Society (WES).[5] To date, no therapy has an optimal benefit/risk profile, which attests to the unmet need for effective therapy for women suffering from endometriosis-associated pain.

3.2 Elagolix

Elagolix sodium (hereinafter "elagolix") is a novel, oral, short-acting, nonpeptide competitive gonadotropin releasing hormone (GnRH) antagonist that is being developed by AbbVie for the management of endometriosis with associated pain and heavy menstrual bleeding associated with uterine fibroids.

3.2.1 Preclinical Experience

3.2.1.1 Toxicology

A detailed discussion of the preclinical toxicology in addition to data on absorption, metabolism, distribution and elimination can be found in the Investigator Brochure.[6]

3.2.2 Clinical Experience

The current Investigator Brochure provides details of the pharmacology and pharmacokinetics of elagolix in humans, in addition to a summary of elagolix clinical studies in Phases 1, 2 and 3.[6]

In two replicate Phase 3 studies in women with endometriosis-associated pain, both elagolix treatment groups (elagolix 150 mg QD and 200 mg BID) met the coprimary efficacy endpoints showing a statistically significant higher proportion of responders for dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) than those who received placebo at Month 3.[7] Persistence of efficacy was observed through Month 6. The 150 mg QD dose demonstrated efficacy in 3 of 7 key ranked secondary outcome measures including significant reductions from baseline with the Daily Diary endometriosis-associated pain score via NRS (at Month 3), DYS (at Month 6) and NMPP (at Month 6). The 200 mg BID dose showed additional statistically significant improvement in all 7 key ranked secondary outcome measures, including reductions in any rescue analgesic agent (NSAIDS or opioids), and dyspareunia scores.

Consistent with estradiol (E2) suppression and previous elagolix studies, there was a dose dependent effect on BMD, such that a longer duration of treatment with the higher elagolix dose (200 mg BID) may require concomitant use of hormonal add back therapy to mitigate BMD loss.

Elagolix is not contraceptive and can change the menstrual bleeding pattern. A folliculogenesis study with elagolix revealed a dose-dependent suppression of ovulation. Elagolix should not be used in women who are pregnant or trying to become pregnant. Information regarding contraception counseling and pregnancy testing is provided in Section 5.2.4.

3.3 Differences Statement

This Phase 3b study will evaluate the safety and efficacy of elagolix 150 mg QD and elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD in 18 to 49 year old

premenopausal women with endometriosis with moderate to severe pain. This study is intended to provide additional dosing guidance for elagolix 150 mg daily over a 2 year treatment period, and dose escalation to 200 mg BID with E2/NETA in incomplete responders. In addition, this study will investigate known modifiable risk factors for BMD decrease to further educate practitioners as to which patients may be at higher risks for BMD decrease. Such information would equip prescribers to safely prescribe elagolix for longer periods of time.

3.4 Benefits and Risks

Clinical studies with elagolix have demonstrated a statistically significant reduction in endometriosis-associated pain in premenopausal women with moderate to severe endometriosis-associated pain, including clinically meaningful improvements in DYS, NMPP, and in some cases, dyspareunia. Elagolix has been administered to over 3,700 subjects to date, and has been generally well tolerated. The most common adverse events associated with its use have included hot flush, headache and nausea.[6] A modest degree of BMD decrease has been associated with elagolix, also in a dose-dependent manner, as expected from its mechanism of action. Hormonal add-back therapy may help to mitigate this effect. Menstrual cycle changes are also observed in individuals administered elagolix, and include lengthening of the cycle, and in some subjects, oligo- or amenorrhea and/or irregular bleeding or spotting. Pregnancies have been observed in subjects exposed to elagolix, which is consistent with the dose-dependent effect on suppression of ovulation.

To date, the benefit/risk profile of elagolix appears to remain favorable for the management of endometriosis-associated pain, and will be further defined by data from this Phase 3 trial.

4.0 Study Objective

The objectives of this study are to:

- Compare the efficacy at Treatment Month 6 of dose escalation to elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD versus continuing elagolix 150 mg QD in subjects who are incomplete efficacy responders to elagolix 150 mg QD at Treatment Month 3
- Assess the effects of elagolix 150 mg QD and elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD on BMD after up to 24 months of treatment
- Evaluate the modifiable and non-modifiable risk factors associated with changes in BMD over 24 months of treatment

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, dose-escalation study designed to evaluate the safety and efficacy of both elagolix 150 mg QD and elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD over 24 months in the management of premenopausal women with endometriosis with moderate to severe pain. After establishing eligibility, the study starts with open-label treatment for the first 3 months. Following the Treatment Month 3 visit and continuing through Month 24, the study is conducted in a double-blinded manner with treatment assignment determined based on the efficacy responder status assessed at Treatment Months 3 and 6.

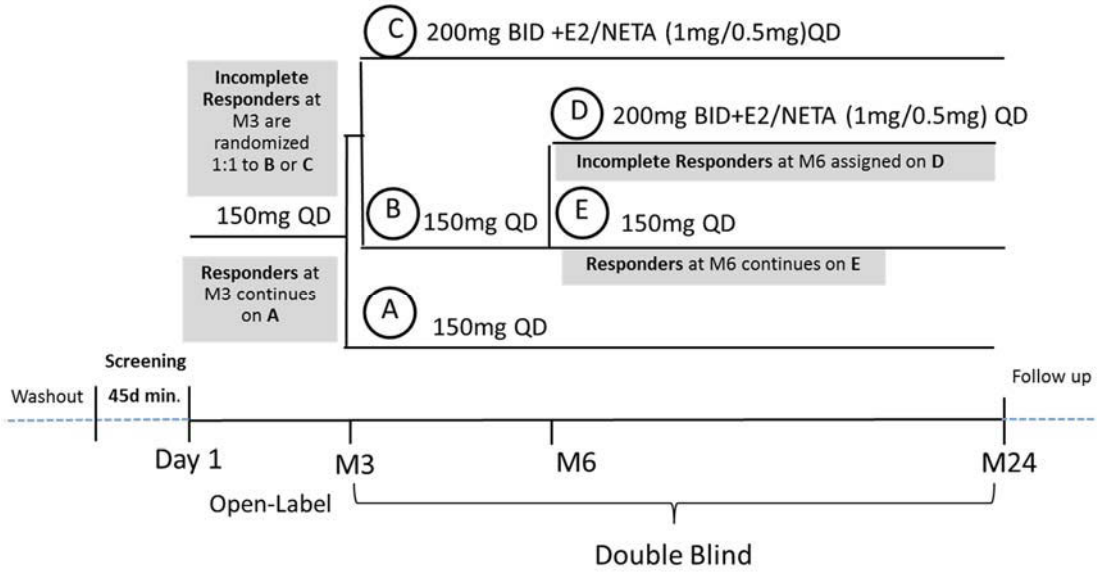
At the Treatment Month 3 study visit, the efficacy responder status of each subject will be determined based on the responses to the Daily Diary endometriosis-associated pain score via NRS collected in the electronic diary (e-Diary). The results of the responder status determination are blinded and the details of the responder status calculation are outlined in Section 5.5.3. Subjects determined to be efficacy responders at the Treatment Month 3 visit will continue to dose with elagolix 150 mg QD in a blinded manner throughout the remainder of the 24-month Treatment Period. Subjects determined to be incomplete efficacy responders at the Treatment Month 3 visit will be randomized in a blinded manner in a 1:1 ratio to receive elagolix 150 mg QD or elagolix 200 mg BID + E2/NETA

(1 mg/0.5 mg) QD. Subjects who were randomized to receive elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD will continue with this treatment in a blinded manner throughout the remainder of the 24-month Treatment Period.

At the Treatment Month 6 study visit, the efficacy responder status of each subject will be determined in the same blinded manner as at the Month 3 study visit. Subjects who randomized at Treatment Month 3 to receive elagolix 150 mg QD and are subsequently determined to be efficacy responders at Month 6 will continue to receive elagolix 150 mg QD throughout the remainder of the 24-month Treatment Period. Subjects who randomized at Month 3 to receive elagolix 150 mg QD and are subsequently determined to be incomplete efficacy responders at Month 6 will receive elagolix 200 mg BID + E2/NETA (1 mg/0.5 mg) QD throughout the remainder of the 24-month Treatment Period.

The study schematic is shown below in Figure 1.

Figure 1. Study Schematic



The Treatment Groups are outlined below:

Day 1 through Month 3 (Open-Label):

- Open-Label elagolix 150 mg QD

Month 4 through Month 6 (Double-Blind):

- **(A)** Efficacy responders to elagolix 150 mg QD at Month 3
- **(B)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3 and randomized to elagolix 150 mg QD treatment group
- **(C)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3 and randomized to elagolix 200 mg BID plus E2/NETA 1 mg/0.5 mg QD treatment group

Months 7 through Month 24 (Double-Blind):

- **(A)** Efficacy responders to elagolix 150 mg QD at Month 3 and continue treatment through Month 24
- **(C)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD treatment group and continue the same treatment through Month 24.
- **(D)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 150 mg QD treatment group and are incomplete efficacy responders at Month 6, and dose increased to elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD through Month 24
- **(E)** Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 150 mg QD treatment group and are efficacy responders at Month 6 continue the same treatment through Month 24

The total duration for this study is approximately 27 to 50 months, consisting of 4 study periods. One month is defined as 28 days.

- Washout Period – up to 10 months prior to Screening (only applicable if subject is taking exclusionary medication at the time of consenting; duration of washout depends on the type of excluded medication being taken)
- Screening Period – approximately 1.5 to 4 months prior to the first dose of study drug.
- Treatment Period – up to a total of 24 month treatment duration consisting of the following:
  - Open-Label Run-In Period: 3 months treatment duration from Day 1 through Treatment Month 3 study visit
  - Double-Blind Active Treatment Period: Treatment Month 3 study visit through Treatment Month 24 study visit
- Follow-up Period – up to 12 months following the last dose of study drug

Details for each Study Period are described below.

Washout Period:

Following informed consent, subjects who have been taking exclusionary medications prior to screening that require discontinuation (washout), must enter the Washout Period. The duration of the required washout period is presented in Table 1. Applicable study procedures may be performed, such as medical, social and gynecological history (including documentation of diagnosis of endometriosis via surgical visualization or histological diagnosis), a brief physical examination with vital signs and urine pregnancy testing; protocol-related adverse event review and documentation of current medications.

Subjects must complete the Washout Period and have had at least 1 menstrual period (menses) prior to entering the Screening Period. Subjects will also begin the use of non-hormonal dual contraception during the Washout Period and receive counseling on the importance of consistent, appropriate and effective use of contraception, and contraceptives dispensed, as necessary.

Screening Period

Following informed consent (if Washout was not required), subjects will enter into the Screening Period. Eligible subjects will have documentation of a surgical confirmation of endometriosis. In addition to medical and gynecological history, specific history will be obtained to help identify potential risk factors/predictors related to changes in BMD, including modifiable and non-modifiable risk factors. The following safety assessments will be completed during the Screening Period:

- dual energy x-ray absorptiometry (DXA) of the lumbar spine total hip and femoral neck to document baseline BMD
- transvaginal ultrasound (TVU) to rule out any clinically significant gynecological disorders such as ovarian cysts, fibroids or endometrial polyps;
- Papanicolau (Pap) test to rule out malignancy or pre-malignant changes;
- endometrial biopsy to rule out endometrial pathology;
- mammogram in subjects 39 years of age or older if one has not been performed within 3 months prior to start of Screening;
- baseline ECG;
- clinical laboratory testing.

An electronic diary (e-Diary) will be provided to subjects to begin recording:

- DYS and NMPP via the 4-point Endometriosis Daily Pain Impact Diary;
- Daily Diary endometriosis-associated pain score via NRS;
- dyspareunia (if applicable) via a 4-point scale and
- the presence and intensity of uterine bleeding.

A minimum of 45 days of daily e-Diary entries are required to be completed during the Screening Period. To be considered eligible for the study, during the last 35 calendar days of the Screening Period, subjects must have:

- at least 2 days of moderate or severe DYS AND

- one of the following:
  - at least 2 days of moderate or severe NMPP with an average NMPP score of at least 1.0, OR
  - at least 4 days of moderate or severe NMPP and an average NMPP score of at least 0.5.

Additionally, subjects must have 2 menstrual cycles with cycle length of 21 – 38 days, and at least 1 full menstrual cycle (i.e., 2 menses or menstrual periods) must be documented in the e-Diary during the Screening Period.

Subjects will be allowed to take protocol-specified analgesic rescue medication for endometriosis-associated pain and will record use daily in the e-Diary. Protocol specific analgesic rescue medication for endometriosis-associated pain will include four equivalent NSAID choices and two equivalent opioid choices.

Use of other rescue analgesic or the use of prophylactic analgesic medications for endometriosis-associated pain is not allowed. The subject and Investigator will decide on the appropriate rescue analgesic medications for that subject (based on the approved options). Subjects are also required to use appropriate non-hormonal methods of contraception.

Subjects who have signed the informed consent and did not complete the Day 1 visit will be considered screen failures. Subjects who initially screen fail for the study may be permitted to re-screen following re-consent. The subject must meet all inclusion and none of the exclusion criteria during re-screening to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

Treatment Period:

The Treatment Period begins with Study Day 1. Study Day 1 will occur between Cycle Days 1 to 10 of a subject's menses (Cycle Day 1 is defined as first day with full menstrual flow) for all subjects who meet eligibility criteria during the Screening Period. On Study Day 1, all subjects will begin open-label dosing with elagolix 150 mg QD. The first dose

of study drug will be administered at the study site on Day 1 and study drug kits will be dispensed to subjects to continue daily dosing. Monthly on-site study visits will be conducted during the first 6 months of the Treatment Period. Subjects will be expected to come in to the site every other month during Treatment Months 7 – 12 and every third month during Treatment Months 13 – 24. Telephone contacts will be conducted at months without an on-site visit. Subjects will be asked to complete various patient-reported outcome (PRO) questionnaires at designated study visits. At the Day 1 visit (prior to dosing) and at all monthly visits (on-site and telephone contacts), site staff will administer to subjects the overall endometriosis-associated pain questionnaire, an 11-point NRS with a 7-day recall period. Starting at Treatment Month 1 and at all on-site study visits thereafter, subjects will complete the Patient Global Impression of Change (PGIC) questionnaire. Pregnancy (serum and/or urine) tests will be performed at each visit throughout the Treatment Period. Urine pregnancy test kits will be provided to subjects for use at home for the study visits when subjects are not required to come into the clinic/site. Subjects will self-administer the tests and report the results to the site at the telephone contact visits. A positive urine pregnancy test result (including those from home pregnancy testing) must be confirmed with a serum pregnancy test. If a serum pregnancy test result is positive at any time during the Treatment Period, study drug will be discontinued.

Subjects will continue to use the daily e-Diary to record DYS, NMPP; dyspareunia; Daily Diary endometriosis-associated pain score via NRS; rescue analgesic use for endometriosis-associated pain and the presence and intensity of uterine bleeding through Treatment Month 6. Throughout the 24-month Treatment Period, all subjects will continue to be allowed to take protocol specified rescue analgesic medication for endometriosis-associated pain. Use of non-protocol specific analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed. Subjects will record the use of protocol specific analgesic rescue medications for endometriosis-associated pain in the daily e-Diary until Treatment Month 6; thereafter, use of protocol specific analgesic rescue medications will be assessed and documented at the study visits.

At designated study visits during the 24-month Treatment Period, blood samples will be collected for clinical safety labs, including vitamin D levels. In addition, blood samples will be collected for assay of serum estradiol, plasma concentrations of elagolix and norethindrone.

BMD will be assessed throughout the Treatment Period. Following baseline, DXA scans will be obtained at Treatment Months 6, 12, 18 and 24. A DXA scan will be required if a subject discontinues at the time of or after the Treatment Month 6 visit or if the reason for premature discontinuation is due to the occurrence of a fracture or any newly diagnosed bone condition.

Vital signs assessments will be conducted at all on-site study visits. Additional safety assessments are completed as appropriate at designated study visits throughout the Treatment Period. Adverse event and concomitant medication review will be conducted at all Treatment Period study visits.

Criteria for Assessment of Subject Status Following the Open-Label Run-In Period:

At the Treatment Month 3 study visit, subjects will be assessed as either an 'efficacy responder' or an 'incomplete efficacy responder' based on responses entered in the e-Diary on the Daily Diary endometriosis-associated pain score via NRS. The status of a subject will be determined within the e-Diary system as follows:

- Efficacy responder: $\geq$ 30% decrease (improvement) from Baseline based on the average of the Daily Diary for endometriosis-associated pain score via NRS over a 35 day window
- Incomplete efficacy responder: < 30% decrease (improvement) from Baseline based on the average of the Daily Diary for endometriosis-associated pain score via NRS over a 35 day window
- Following conclusion of the Open-Label Run-In Period, treatment arm assignment for all subjects will become and remain blinded for the remainder of the 24-month Treatment Period. The assessment of responder status is also blinded.

At the Treatment Month 3 study visit, any subjects that have zero entries for the Daily Diary for endometriosis-associated pain score via NRS during the 35 day window prior to the study visit will continue dosing with 150 mg QD for the remainder of the treatment period (will be assigned to Group A).

Dose Escalation During the Treatment Period:

Subjects assessed as "efficacy responders" (as defined above) will be assigned to continue dosing with elagolix 150 mg QD (Group A) in a blinded manner via Interactive Response Technology (IRT). All other subjects assessed as "incomplete efficacy responders" will be assigned randomly (in an equal ratio) via IRT to either elagolix 150 mg QD (Group B) or elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (Group C) for 3 months. To preserve the blind, IRT will be utilized for study drug assignment for all subjects. The first dose from the newly assigned study drug kit at Treatment Month 3 will be administered at the site. The pharmacokinetic and pharmacodynamics samples must be obtained prior to study drug administration at the Treatment Month 3 visit.

At the Treatment Month 6 study visit, in a blinded manner via IRT, all subjects who were incomplete efficacy responders and randomly assigned at Treatment Month 3 to elagolix 150 mg QD will again be assessed for efficacy response in the same manner as was done at the Treatment Month 3 visit. All subjects in this group (Group B) who become efficacy responders will continue dosing with elagolix 150 mg QD in a blinded manner (Group E). All other subjects in this group who are assessed as incomplete efficacy responders at Month 6 will escalate dosing to elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (Group D). To preserve the blind, IRT will be utilized for treatment assignment of all subjects; however, only subjects randomly assigned at Treatment Month 3 to the elagolix 150 mg QD (Group B) will have a chance for dose modification. The first dose from the newly assigned study drug kit at Treatment Month 6 will be administered at the site. The pharmacokinetic and pharmacodynamics samples must be obtained prior to study drug administration at the Month 6 visit.

At the Treatment Month 6 study visit, any subjects that have zero entries for the Daily Diary for endometriosis-associated pain score via NRS during the 35 day window prior to the study visit will continue dosing on the current dose assignment for the remainder of the treatment period.

The treatment assignments following the Treatment Month 6 study visit will continue for all subjects for the duration of the 24-month Treatment Period in a blinded manner. There will not be further dose adjustments following the Treatment Month 6 visit for any subject.

BMD Assessment and Subject Specific Safety Stopping Criteria for BMD During the Treatment Period:

DXA scans of the lumbar spine, total hip and femoral neck will be obtained at Treatment Months 6, 12, 18 and 24. If the results of any post-baseline DXA prior to the Treatment Month 24 timepoint, as read by the central imaging vendor selected for the study, document a Z-score (for subjects < 40 years of age at the time of the Screening DXA) or a T-score (for subjects ≥ 40 years of age at the time of the Screening DXA) of < –2.5 in the lumbar spine, total hip or femoral neck, or a BMD decrease from bseline of > 8% in the lumbar spine, total hip or femoral neck, the subject must be discontinued from study drug dosing and will enter the Follow-Up Period.

Follow-Up Period:

Subjects will enter the Follow-Up Period for up to 12 months to assess bone recovery after up to 24 months of treatment with the study drug. Subjects who prematurely discontinue (PD) from the study at the time of or after the Treatment Period Month 6 visit, or who PD due to occurance of a fracture or newly diagnosed bone condition will enter the Follow-Up Period.

DXA scans will be obtained at designated visits as described in Appendix C. Additional study procedures will be performed at designated study visits as outlined in Appendix C.

Adverse event collection is detailed in Section 6.1.4 and Appendix C. Concomitant medication use will be reviewed at all study visits.

The Follow-Up Period for the study should conclude for all subjects approximately 30 days after the last completed Treatment Month 24 visit.

Additional detail regarding study procedures during the Follow-Up Period is provided in Appendix C, Study Activities.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

1. Subject has voluntarily signed and dated the informed consent form (ICF), approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to washout (if applicable), or initiation of any screening or study-specific procedures.
2. Subject is a premenopausal female 18 to 49 years of age (inclusive) at the time of Screening.
3. Subject has a documented surgical diagnosis (e.g., laparoscopy or laparotomy) of endometriosis established by visualization or histology within 10 years prior to entry into Washout or Screening.
4. Subject must agree to use only those rescue analgesics permitted by the protocol during the Screening and Treatment Periods for her endometriosis-associated pain.
5. Subject has a negative urine and/or serum pregnancy test(s) during the Washout (if applicable) and/or Screening Periods, and a negative urine pregnancy test just prior to administration of the first dose of study drug.
6. Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Washout (if applicable), Screening, Treatment and through the end of Month 1 of the Follow-Up Period. Acceptable methods of dual contraception include the following combinations:

- Condom with spermicide (e.g., 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)
- Vaginal sponge impregnated with spermicide and used with a condom.

Subject is not required to use dual contraception methods if:

- Sexual partner(s) is (are) vasectomized, at least 6 months prior to Screening
- Subject practices total abstinence from sexual intercourse as the preferred lifestyle of the subject; however, periodic abstinence requires use of dual contraception.
- Subject had a bilateral tubal ligation, bilateral tubal occlusion or bilateral salpingectomy at least 4 months prior to the start of Screening
- Subject is not sexually active with men; however, periodic sexual relationship(s) with men require the use of study defined dual non-hormonal contraception.

7. Subject ≥ 39 years of age at entry into screening has a normal mammogram during Screening or within 3 months prior to the start of Screening (BI-RADS Classification 1 to 2 or equivalent).
8. Prior to Study Day 1, subject has two documented menstrual cycles with a cycle length of 21 – 38 days. A minimum of one full menstrual cycle (i.e., including 2 menses or periods) must be documented in the e-Diary; however, the start of the previous menstrual cycle may be based on the subject's historical recall and must be appropriately recorded in the subject's source documents.
9. Subject has a minimum of 45 days of e-Diary entries during the Screening Period.
10. Subject has the following documented in the e-Diary during the last 35 days prior to Study Day 1:

    - At least 2 days of "moderate" or "severe" DYS
      AND one of the following:

- At least 2 days of "moderate" or "severe" NMPP and an average NMPP score of at least 1.0,

  OR

- At least 4 days of "moderate" or "severe" NMPP and an average NMPP score of at least 0.5.

Rationale for Inclusion Criteria

5.2.2 Exclusion Criteria

1. Subject is pregnant or breastfeeding, or is planning a pregnancy during the duration of study participation (potentially up to 50 months; inclusive of the Washout, Screening, Treatment and Follow-Up Periods).
2. Subject is less than 6 months postpartum or 3 months post-abortion (spontaneous or elective), prior to the start of Screening.
3. Subject has an intra-uterine device (IUD) or contraceptive sub-dermal implant. If the IUD or sub-dermal implant is removed and subject completes the appropriate washout, subject may be screened for the study.
4. Subject has a surgical history of:
   - Hysterectomy (with or without oophorectomy)

- Bilateral oophorectomy
- Any major surgery (including laparotomy for endometriosis) within 3 months OR endometrial ablation within 6 months OR minor surgery (including laparoscopy for endometriosis) within 1 month prior to the Screening visit.

5. Subject has a history of previous non-response to GnRH agonists, GnRH antagonists, depo-medroxyprogesterone acetate (DMPA), or aromatase inhibitors as assessed by subject report of no improvement in DYS or NMPP (subject report of partial response to or side effects from these agents is not exclusionary).
6. Subject has any of the following identified on the Screening TVU or endometrial biopsy:
   - A simple ovarian cyst > 5 cm in longest diameter that persists on repeat TVU
   - A complex ovarian cyst > 3.5 cm in diameter (longest diameter) that persists on repeat TVU
   - An endometrioma > 3.5 cm in diameter (longest diameter)
   - Large endometrial polyp ≥ 1 cm (confirmed by SIS and/or office hysteroscopy)
   - Single fibroid ≥ 4 cm
   - Multiple fibroids (> 4) that measure ≥ 2 cm
   - Symptomatic submucousal fibroid of any size
   - Any other clinically significant gynecologic condition or endometrial pathology.
7. Subject has a Screening Pap test result showing any evidence of malignancy or pre-malignant changes.
8. Subject has a current history of undiagnosed abnormal uterine (vaginal or genital) bleeding.
9. Subject has a hypersensitivity, documented allergy or is unable to tolerate norethindrone, norethindrone acetate or estradiol.
10. Subject is unable or unwilling to discontinue use of any prior analgesics on entry into the Screening Period or if a subject has a clinically significant sensitivity,

allergy to, or any other reason that in the Investigators opinion that would prevent the subject from using any of the protocol allowed rescue analgesic medications.

11. Subject is unable or unwilling to discontinue use of medical treatments for endometriosis on entry into the Washout or Screening Period.

12. Subject has chronic pelvic pain that is not caused by endometriosis (e.g., interstitial cystitis, adenomyosis [as a dominant condition diagnosed by MRI or ultrasound], fibroids, pelvic inflammatory disease [PID], non-endometriosis-related pelvic adhesive disease, irritable bowel syndrome), that requires chronic analgesic therapy, which would interfere with the assessment of endometriosis-related pain.

13. Subject has any other chronic pain syndrome (e.g., fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headaches) that requires chronic analgesic or other chronic therapy, which, in the opinion of the Investigator, would interfere with the assessment of endometriosis-related pain.

14. Subject is using any systemic corticosteroids for over 14 days within 3 months prior to Screening or is likely to require treatment with systemic corticosteroids during the course of the study. Over-the-counter and prescription topical, inhaled or intranasal corticosteroids are allowed.

15. Subject has a history of any of the following:
    - Major depression or post-traumatic stress disorder (PTSD) within 2 years of the Screening visit
    - Other major psychiatric disorder at any time (e.g., schizophrenia, bipolar disorder)

16. Subject has a history of suicide attempts or answered "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening or prior to enrollment on Day 1.

17. Subject has clinically significant abnormalities in clinical chemistry, hematology or urinalysis, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT) or bilirubin (unless known diagnosis of Gilbert's syndrome) ≥ 3.0 times the

upper limit of the reference range or a serum creatinine > 2.0 mg/dL at Screening. Clinically significant laboratory abnormalities may be retested 1 time prior to Day 1; however, the results must meet entry criteria prior to study drug administration on Day 1.

18. Subject has a reactive or positive Screening test result for Hepatitis A Virus Immunoglobulin M (HAV IgM), Hepatitis B Surface Antigen (HBsAg) or Hepatitis C Virus Antibody (HCV Ab) or Human Immunodeficiency Virus (HIV) or HIV Antibody (HIV Ab).

19. Subject used any known moderate or strong inducers of cytochrome P450 3A (CYP3A) (e.g., phenobarbital, rifampin, carbamazepine, St. John's Wort) as indicated in Table 2 within 1 month prior to Day 1.

20. Subject has a clinically significant abnormal electrocardiogram (ECG) at Screening.

21. Subject has any condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, spinal hardware, severe scoliosis or weight) or any history of osteoporosis or other metabolic bone disease or including:
    - Intercurrent bone disease (e.g., osteomalacia, osteogenesis imperfecta)
    - History or presence of an unstable condition that is associated with a decrease in BMD (e.g., uncontrolled hyperthyroidism, uncontrolled hyperparathyroidism, anorexia nervosa)
    - History of low-trauma hip or vertebral fractures (e.g., fracture resulting from a fall from a standing height or lower)
    - Bilateral hip replacement
    - Clinically significant hypocalcemia, hypo- or hyperphosphatemia, including during Screening (lab results)
    - Treatment with medication (excluding calcium and Vitamin D) for bone disease associated with a decrease in BMD.

22. Screening DXA results of the lumbar spine (L1 – L4), femoral neck or total hip BMD corresponding to less than 2.0 or more standard deviations below normal

(Z-score < –2.0 for subjects < 40 years of age, T-score for subjects ≥ 40 years of age).

23. Subject has a history of or active malignancy (with or without systemic chemotherapy), except treated basal cell carcinoma of the skin.

24. Subject has either:

- a newly diagnosed, clinically significant medical condition that requires therapeutic intervention (e.g., new onset hypertension), that has not been stabilized 30 days prior to enrollment on Day 1 OR
- a clinically significant medical condition that is anticipated to require intervention during the course of study participation (e.g., anticipated major elective surgery) OR
- an unstable medical condition that makes the subject an unsuitable candidate for the study in the opinion of the Investigator, (including, but not limited to, uncontrolled diabetes mellitus, uncontrolled hypertension, epilepsy requiring anti-epileptic medication, unstable angina, confirmed inflammatory bowel disease, hyperprolactinemia, clinically significant infection or injury).

25. Subject has any conditions contraindicated with use of E2/NETA such as:

- Current or history of deep vein thrombosis (DVT) or pulmonary embolism
- Current or history (within 1 year of screening) of arterial thromboembolic disease (e.g., stroke, myocardial infarction).

26. Subject has a history of drug and/or alcohol abuse within 1 year prior to Screening. A history of legal recreational or medicinal cannabinoid/marijuana use is not exclusionary.

27. Subject was previously enrolled (randomized) in either an elagolix study or a study involving another investigational GnRH antagonist, less than 1 year prior to entry into the Screening period.

28. Subject is currently participating in another investigational study (drug or device) or has participated in an investigational drug study within 2 months prior to the Screening Visit. If a subject has participated in an investigational trial with

hormonal treatment, the minimal washout period must be completed prior to entering the Screening Period for this study.

29. In the judgment of the Investigator, subject is an unsuitable candidate to receive elagolix or E2/NETA or will be unable or unwilling to comply with study-related assessments and procedures, including completion of the e-Diary and consistent use of non-hormonal dual contraception throughout the required time period.

Rationale for Exclusion Criteria

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of consent, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

If there are any questions regarding concomitant or prior therapies the AbbVie Therapeutic Area Scientific Director should be contacted who will then discuss with the AbbVie Therapeutic Area Medical Director (TA MD) and provide a recommendation.

5.2.3.1 Prior Therapy

To document historical use, any medication administered to treat endometriosis or endometriosis-associated pain prior to Washout or Screening will be recorded in source documents and the electronic case report forms (eCRFs). The date(s) of administration (including start and treatment end dates), and reason for use and discontinuation must be recorded in source documents and eCRFs.

Subjects using or who have used hormonal contraception or other hormonal/anti-hormonal therapies may be considered for study participation provided they complete the required washout (Washout Period) and have had at least 1 menstrual period (menses) before entering into the Screening Period. Subjects currently using hormonal/anti-hormonal therapies will sign an ICF before they discontinue these medications and begin the washout. Subjects who discontinued taking hormonal contraception or other hormonal/anti-hormonal therapies before they were approached to participate in the study must sign the ICF and complete the remainder of the washout and have had at least 1 menstrual period (menses) before entering the Screening Period. Discontinuation of hormonal contraception should be done according to prescribing information (e.g., complete current cycle of birth control pills) and per the investigator's clinical judgement.

The minimum washout intervals for hormonal/anti-hormonal therapies prior to entering Screening are described in Table 1. Subjects may enter the Screening Period after the required washout has been completed and documentation of at least 1 menstrual period. Subjects who have an IUD or contraception sub-dermal implant and agree to have the IUD or sub-dermal implant removed must complete the washout period described in Table 1 and have had at least 1 menstrual period prior to entering Screening.

If the type of hormonal product and the length of Washout are not listed in the table below, consult AbbVie Therapeutic Area Scientific Director who will discuss with the AbbVie TA MD and provide a recommendation.

Table 1. Washout Intervals for Exclusionary Hormonal/Anti-Hormonal Therapy

Therapy	Minimum Interval for Washout* (Prior to Initial Screening Visit)
Medroxy progesterone acetate injection (Depo-Provera®; Sayana®)	10 months from injection
GnRH agonist 3 month depot (Lupron Depot® 11.25 mg), goserelin acetate (Zoladex®)	6 months from injection
Synarel® (Nasal Spray)	4 months
GnRH antagonist (parenteral)	3 months
Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate, Vilaprisan)	
Nafarelin acetate	
Danazol (Cyclomen®)	
Aromatase inhibitors	
Oral contraceptives**	1 month
Oral, transdermal or intravaginal estrogen preparations	
Oral, intravaginal or transdermal progesterone/progestin preparations***, including tibolone	
GnRH agonist – 1 month depot (including Lupron Depot® 3.75 mg)	
Hormonal and Non-Hormonal IUD, sub-dermal progestin implant (e.g., Nexplanon®)	1 month after removal
NuvaRing®	

* This is the minimum washout; however, subjects may not enter Screening until at least 1 menstrual cycle has occurred during the Washout Period. If less than a full course of therapy is administered, the Investigator should contact their Monitor who will discuss with the AbbVie TA Scientific Director/MD and confirm the required washout interval.

** Subjects must complete the mandatory month of washout from oral contraceptives and subsequently have a menses/period. Bleeding due to withdrawal of the oral contraceptives cannot be considered the required menses/period.

*** Exception: levonorgestrel 1.5 mg or ulipristal acetate 30 mg used for emergency contraception.

5.2.3.2 Concomitant Therapy

All concomitant medications taken (except protocol specific rescue analgesic medications [Section 5.2.3.4] taken for endometriosis- associated pain, which are recorded in the e-Diary during Screening and the first 6 months of Treatment) during the duration of study participation (Washout [if required], Screening, Treatment, Follow-Up) must be recorded in source documents and eCRFs, along with the reason for use, dates of administration, dosages, routes and frequency.

The following concomitant medications are allowed during study participation, as these medications are not expected to meaningfully confound the efficacy evaluation, nor are there substantial safety concerns with concomitant use:

- Inhaled corticosteroids for treatment of asthma or similar airways diseases
- Over-the-counter and prescription topical, intranasal or local injectable (for occasional use) corticosteroids
- Vaccines
- Triptans or ergotamines for the treatment of infrequent migraine headaches
- Multivitamins
- Anti-depressants
- Non-opioid analgesics (e.g., NSAIDs) may be used for conditions other than endometriosis-associated pain (e.g., acute conditions such as headache or fever)
- Levonorgestrel or ulipristal acetate only when used as emergency contraception (e.g., Plan B®)

5.2.3.3 Prohibited Therapy

All hormonal forms of birth control (except the emergency contraceptive pill, levonorgestrel 1.5 mg [such as Plan B®], or ulipristal acetate 30 mg [such as Ella® or EllaOne®]) are prohibited during Washout, Screening, Treatment and until the Follow-Up Month 1 visit. Subjects may start hormonal contraception after completion of Follow-Up

Month 1, provided that the subject has a documented menstrual period (menses) after the Treatment Period and prior to that visit. For subjects who are prescribed/administered the emergency contraceptive pill during the study, the information should be captured in the source documents and eCRF.

To protect subject safety and to minimize confounding the study results, the following concomitant medications are prohibited during the study as specified below:

Table 2. Prohibited Medications

Prohibited During the Washout, Screening, Treatment, and Follow-Up Periods	
GnRH analogues	Leuprolide acetate (Lupron®) GnRH agonist: nafarelin acetate (Synarel®), goserelin acetate (Zoladex®) GnRH antagonists (other than elagolix) Medroxyprogesterone Acetate (Depo-Provera®, Provera®)
Prohibited During the <u>Washout, Screening and Treatment Periods and thru Follow-Up Month 1</u>	
Hormonal Medications and Non-hormonal Estrogen Supplements, such as:	Danazol (Danocrine®, Cyclomen®) Oral contraceptives Other progestins (oral, vaginal, IUDs, implantable) Levonorgestrel (except emergency contraception, i.e., levonorgestrel 1.5 mg) Spironolactone Mifepristone Ulipristal acetate (except emergency contraception, i.e., ulipristal acetate 30 mg) Testosterone preparations Tamoxifen Bromocriptine (Parlodel®) Cabergoline (Dostinex®) Raloxifene (Evista®, Optruma, or generics) Bazedoxifene (Conbriza) Aromatase Inhibitors (e.g., Anastrozole [Arimidex®], Exemestane [Aromasin®]) Natural Estrogen preparations or herbal remedies/supplements to treat premenstrual or gynecological problems (e.g., soy-containing supplements, black cohosh)

Table 2. Prohibited Medications (Continued)

Prohibited During the <u>Screening and Treatment Periods</u>	
Immediate Release (IR) Opioid Analgesics, such as:	Oxymorphone Hydromorphone Morphine Buprenorphine *Except for short-term use as noted below and protocol specified rescue opioid analgesics*
Long-acting, Controlled Release (CR), Extended Release (ER) or Transdermal Opioid Analgesics, such as:	CR/ER Morphine CR/ER Hydromorphone CR/ER Oxymorphone CR/ER Oxycodone ER Tapentadol ER Tramadol Fentanyl Methadone Levorphanol Buprenorphine
Intravenous Analgesics, such as:	Fentanyl Morphine Buprenorphine
Synthetic Prostaglandin E1 Analogs, such as:	Misoprostol (Cytotec®, Arthrotec®) *These medications may influence bleeding and should not be taken during the time noted above. However, use for the endometrial biopsy procedure is permitted, if needed.*
Cannabinoids	Including any marijuana use
Prohibited <u>1 Month Prior to Day 1 and During the Treatment Period</u>	
Moderate or strong CYP3A[8] Inducers, such as:	**Moderate Inducers:** Bosentan Efavirenz Etravirine Modafinil Nafcillin **Strong Inducers:** St. John's Wort Rifampin Carbamazepine Phenytoin Dexamethasone (chronic use)

Table 2. Prohibited Medications (Continued)

Prohibited During the Screening, Treatment, and Follow-Up Periods	
Osteoporosis Medications (Bisphosphonates, RANKL Inhibitors, Anabolic Bone Agents or rPTH), such as:	denosumab, teriparatide Fosamax®, Boniva®, Reclast®, XGEVA®, Forteo®
Glucocorticoids/Corticosteroids, systemic administration (oral, IM or IV)	*Except for short-term use as noted below.*
Other Teratogens, such as:	Topiramate, Accutane® and other oral retinoids

Legal recreational or medicinal use of cannabinoids/marijuana prior to Washout or prior to Screening is not prohibited; however any use of cannabinoids/marijuana during study participation is prohibited.

Analgesic medications used to specifically treat endometriosis-associated pain, other than the protocol-specified allowable rescue medications outlined in Section 5.2.3.4 are not permitted during the study (Screening and Treatment Periods). Prophylactic use (i.e., on a standing basis or for prevention of pain) of any analgesics for endometriosis-associated pain (including protocol specified rescue analgesics) is likewise prohibited.

Short-term use (no longer than 2 weeks (total of 14 days) per occurrence) of immediate-release opioids/opioid-containing products or systemic glucocorticoids/corticosteroids to manage acute conditions not related to endometriosis-associated pain is allowed during the Treatment Period. A maximum of 6 weeks (total of 42 days) over the 24 month Treatment Period is allowed during a subject's participation. If the subject requires > than 2 weeks duration per occurrence or > 6 weeks (total of 42 days) over the 24 month Treatment Period, their continued participation in the study must be reviewed with the AbbVie TA Scientific Director/MD.

If a prohibited medication is necessary to treat an adverse event or a pre-existing condition other than endometriosis, it should be documented in the subject's source and eCRF. If a subject's use of prohibited medication continues during the study, her continued participation will be evaluated by the Investigator and the AbbVie TA

Scientific Director/MD. If there are any questions regarding prior or concomitant therapy, please contact AbbVie TA Scientific Director.

5.2.3.4 Rescue Therapy

The protocol-allowed analgesic rescue therapies for endometriosis-associated pain are presented in Table 3. Investigators will prescribe a specific analgesic rescue medication from each medication class for subjects at the time of entry into the Screening Period, taking into consideration the subject's preference and/or historical use of analgesics and the Investigator's clinical judgement.

Investigators are not to suggest or advise subjects on any modifications to their rescue medication regimen. Subjects will be instructed to contact the site if a change in their rescue analgesic medication is needed, such that appropriate adjustments can be considered. Investigators may then prescribe a different analgesic rescue medication (from each medication class if necessary) for the subject. Investigators should not prescribe more than one analgesic rescue medication from the same medication class at one time. The dosage form outlined in Table 3 must be utilized, but all prescribed use of rescue analgesic medication should be according to appropriate clinical practice standards and the Investigator's clinical judgment.

Subjects will record use of the protocol-specific rescue analgesic medications taken for endometriosis-associated pain daily in the e-Diary during Screening through the first 6 months of the Treatment Period. This will include the total number of pills/tablets taken for each category of rescue analgesic medication within a 24-hour period. During Treatment Period Months 7 – 24, when the e-Diary is not in use, the use of protocol-specific rescue analgesic medications by the subject will be elicited by site staff at study visits and recorded in the source documents and eCRF. Site staff will be expected to review use of protocol-specific rescue analgesic medications taken by the subject for endometriosis-associated pain throughout the Screening and Treatment Periods.

Prophylactic use of protocol-specific rescue analgesic medications is not allowed. Use of any other analgesic medications for endometriosis-associated pain, including prophylactically, is not allowed from the start of the Screening Period through the 24-month Treatment Period. However, if other analgesic medication for treatment of endometriosis-associated pain is used or if protocol specified rescue analgesics are used for other acute conditions/reasons (e.g., headache, fever, joint pain), such usage will be recorded in the source and eCRF, not in the e-Diary.

If a subject continues to take analgesic(s) other than the protocol-specified rescue analgesics for endometriosis-associated pain, her continued participation in the study will be evaluated by the Investigator and the AbbVie TA Scientific Director. If there are any questions regarding rescue therapy, please contact your Monitor.

Table 3. Permitted Rescue Therapy for Endometriosis-Associated Pain

Medication Class	Medication Name	Dosing Strength*	Country
NSAIDS	Naproxen#	200 mg	All
NSAIDS	Ibuprofen	200 mg	All
NSAIDS	Diclofenac^	25 mg	All
NSAIDS	Celecoxib	50 mg	All
Opioid Analgesics	Hydrocodone + acetaminophen	5 mg Hydrocodone + 300 or 325 mg acetaminophen	US and PR
Opioid Analgesics	Codeine phosphate + acetaminophen$	30 mg codeine + 300 mg acetaminophen$	All

* Use of these rescue analgesic medications should be according to appropriate clinical practice standards and Investigator's clinical judgment.

\# Naproxen 200 mg is equivalent to naproxen sodium 220 mg.

^ Diclofencac Immediate-Release product is preferred.

$ Combination with or without caffeine is permitted.

5.2.4 Contraception Recommendations and Pregnancy Testing

Investigators and study staff will be trained by the Sponsor on the importance of contraception in this clinical trial. Subjects (excluding those subjects who have had a bilateral tubal ligation, bilateral tubal occlusion or bilateral salpingectomy) will be

counseled by the Investigator or designated study staff at every visit throughout study participation on the importance of pregnancy prevention and the use of appropriate and effective methods of contraception.

Subjects must agree to use two forms of non-hormonal contraception (dual contraception) consistently throughout the Washout (if applicable), Screening and Treatment Periods, and the first month of the Follow-Up Period, except as noted below.

Acceptable methods of dual non-hormonal contraception include the following combinations:

- Condom with spermicide (e.g., 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)
- Vaginal sponge impregnated with spermicide; used with a condom

Subjects are not required to use dual contraception methods if:

- Sexual partner(s) is vasectomized at least 6 months prior to Screening.
- Subject had a bilateral tubal ligation, bilateral tubal occlusion or bilateral salpingectomy at least 4 months prior to the start of Screening.
- Subject is not sexually active with men; however, periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as indicated above.
- Subject practices total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence requires use of dual contraception.
- Subject has begun the use of hormonal contraception after the Follow-Up Month 1 visit.

Subjects may begin the use of hormonal contraception after the Follow-Up Month 1 visit, provided she has a negative urine pregnancy test 1 month off of study drug and has returned to menses. If the Subject has not returned to menses by Follow-Up Month 1, the

Investigator would use acceptable medical practice to reinitiate hormonal contraceptive (e.g., pregnancy test, serum FSH, induction of withdrawal bleed).

The following measures will be taken to help promote pregnancy prevention during the study.

1. The informed consent form will include an attestation requiring the subject to confirm in writing (via signature) her full awareness that the potential risks of study drug on the unborn child are unknown and therefore she must not get pregnant during the entire time of study participation, and that she agrees to consistently use protocol required non-hormonal contraception throughout her study participation.
2. The Investigator or designated study staff will counsel the subject that the study drug is not contraceptive, that ovulation may occur even though the study drug may have altered menstrual cycle patterns, and that fetal abnormalities have been reported in pregnant women who have received elagolix in clinical studies; however, it is unknown whether these abnormalities were the result of taking elagolix.
3. The Sponsor will provide training materials to the sites for instructing subjects on the types of protocol-allowed contraception methods, their effectiveness and proper use.
    - The Sponsor will provide all investigative sites with a supply of materials to promote pregnancy prevention, including contraceptives (e.g., condoms and spermicides) to provide to subjects at no charge.
    - Subjects will be allowed to choose an acceptable contraception method of their choice from the contraceptive options provided by the Sponsor and will be expected to consistently practice the allowable methods of contraception. The site will assess the subject's basic understanding of proper contraceptive use through discussion and demonstration of proper techniques (as needed).
    - The site will provide contraceptives and other supplies (e.g., lubricants) to subjects throughout the Washout (if applicable), Screening, and Treatment Periods through Follow-Up Month 1 as needed.

- The source documents will capture the date initial contraception counseling was performed, whether the subject meets protocol criteria for not requiring use of dual contraception, and the type of contraceptive provided to the subject (as applicable). At subsequent study visits, the source documents will capture if there was a change in contraceptive method and whether additional contraceptives were provided to the subject.
- The subject will be asked to attest by signature in a stand-alone attestation form at all on-site study visits (except as noted below) that allowable methods of contraception, as described during the pregnancy prevention counseling, are being practiced.
- For subjects who have had a bilateral tubal ligation, or bilateral tubal occlusion (including Essure®) or bilateral salpingectomy attestation is only required to be collected once during the study prior to enrollment, ideally at the time of consent. Additionally, these subjects do not require contraception counseling at any study visit or the associated documentation of that counseling.

4. The e-Diary will be designed to include a daily reminder to use non-hormonal contraception during screening and up to Treatment period Month 6
5. Monthly study contacts are used to promote frequent interaction with site staff and opportunities for continued education.
6. At each Treatment Period visit (on-site and telephone contacts), the proper use of contraception will be reinforced to address possible ineffective use and the risk of unexpected pregnancy due to unprotected sexual activity.

Pregnancy Testing

Urine and serum pregnancy tests will be performed as specified in Appendix C in all subjects regardless of sexual activity status or method of contraception, including subjects who are surgically sterilized.

The urine pregnancy test result on Day 1 must be reviewed and confirmed to be negative prior to study drug dosing. Prior to performing an endometrial biopsy, the subject must have a confirmed negative urine pregnancy test. In addition, at onsite visits during the

Treatment Period, the urine pregnancy test must be negative prior to providing subjects with their next supply of study drug.

Home urine pregnancy test kits will be provided to subjects during the Treatment and Follow-Up Periods for use at home when subjects are not required to come into the clinic/site (e.g., telephone contact visits and prior to certain study procedures). Subjects will self-administer the tests and report the results to the site during telephone contacts. Subject reported test results will be entered into the source and eCRF.

A positive urine pregnancy test result (including a home urine pregnancy test) must be confirmed with a quantitative serum pregnancy test. The subject should temporarily discontinue study drug administration while waiting for the results of the serum pregnancy test. If a serum pregnancy test result is positive at any time during the Treatment Period, the site will immediately inform the subject to discontinue study drug dosing (Section 5.4.1). If a subject is confirmed as pregnant, the subject will be prematurely discontinued from the study.

If the subject becomes pregnant at any time after baseline up through 30 days post last dose of study drug, an ultrasound examination will be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery. Refer to Section 6.1.6 for instructions on reporting a pregnancy to the Sponsor and the required follow-up on the subject's fetus, pregnancy outcome and infant.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Procedures

The study procedures outlined in Appendix C are discussed in detail in this section, with the exception of study drug dispensing/compliance/accountability (Section 5.5.7), contraception counseling/contraceptive dispensing (Section 5.2.4), the collection of concomitant medication (Section 5.2.3), randomization (Section 5.5.3) and adverse event information (Section 6.0). All study data will be recorded on the eCRFs with the exception of the e-Diary, select PRO data and data from central lab/imaging vendor.

The Screening Period will occur within approximately 1.5 to 4 months prior to administration of the first dose of study drug on Day 1. For procedures repeated during the Screening Period (as allowed per protocol or at the discretion of the AbbVie TA Scientific Director/MD), the procedure performed closest prior to dosing will serve as a baseline for clinical assessment.

Scheduled monthly visits during the Treatment and Follow-Up Periods are based on a 28-day month. All scheduled study visits during the Treatment and Follow-Up Periods should occur within ± 5 days of the scheduled date. However, the TVU, DXA scan, Pap test and endometrial biopsy may be performed within approximately ± 15 days around the associated scheduled Treatment Month visit.

This protocol provides recommendations regarding the sequence of procedures to be performed during the study. In no case should these recommendations outweigh clinical judgment or standard of care. If the protocol indicates that the AbbVie TA Scientific Director is to be contacted prior to performing a procedure, yet the timing of the request would either interrupt a procedure or would interfere with standard of care and clinical judgment, then clinical judgment should prevail and the AbbVie TA Scientific Director should be notified afterwards.

Informed Consent

The IRB/IEC approved informed consent will be signed by the subject before discontinuing any hormonal contraception/therapies or other prohibited medications or

performing any study-specific procedures. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Subjects who have signed informed consent and did not enroll on Day 1 because they either did not complete the Washout Period (if applicable), did not complete the study-specific procedures during the Screening Period or did not meet all entry criteria will be considered Screen Failures. The reason(s) for screen failure will be recorded in the source documents and will be captured in the eCRF.

Medical/Social History

A complete medical history, including documentation of any clinically significant medical conditions, procedures and applicable medications (Section 5.2.3.1), history of tobacco and alcohol use will be collected during the Washout Period (if applicable) or during the Screening Period for those subjects who do not require washout. The medical history will be reviewed and should be updated if significant clinical findings are noted on Day 1 prior to dosing and will serve as the baseline for clinical assessment.

Gynecological and Endometriosis History

A gynecological and endometriosis history will be collected either during the Washout Period (if applicable) or during the Screening Period for those who do not require washout.

The gynecological and endometriosis history will be reviewed and should be updated if needed prior to dosing on Day 1 and will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will include height (at Screening only) and weight measurements (the subject should wear lightweight clothing and not wear shoes).

A brief, symptom-directed physical examination will be performed at Washout (if applicable).

Visits requiring either the complete physical examination (including weight) or a brief, symptom-directed physical examinations are outlined in the Study Activities Table in Appendix C.

Clinically significant physical examination findings prior to study drug dosing on Day 1 will be recorded as medical or gynecological history. Any clinically significant physical examination findings after initiation of dosing will be recorded in the source documents and in the eCRFs as adverse events. The complete physical examination performed during Screening will serve as the baseline for clinical assessment.

Gynecological Examination

A complete breast and pelvic examination, including external genitalia, will be performed during the Screening and Treatment periods as listed in Appendix C. Timing of brief symptom-directed gynecologic examinations are outlined in Appendix C, but may also be performed at any time throughout the study as deemed clinically necessary. The complete breast, pelvic and external genitalia examination completed during Screening will serve as the baseline for clinical assessment.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be conducted during the Screening Period. The ECG should be obtained prior to any blood collection.

For any abnormal screening test results, the ECG may be repeated one time prior to/on Day 1, however the subject may not be enrolled if any clinically significant findings are noted on the repeat ECG. Final results (i.e., results used to determine eligibility) will be entered into the eCRF.

The Investigator or qualified designee at the study site will determine if any findings are clinically significant (in consultation with a cardiologist, if necessary), and document this on the ECG tracing/report, sign and date it. The original ECG tracing or a certified copy

of the original tracing with the physician's assessment will be retained in the subject's source records at the study site.

Vital Signs

Vital sign determination of heart rate, blood pressure, respiratory rate, and body temperature will be obtained at all visits during the study as indicated in Appendix C. The blood pressure, heart rate, and respiratory rate measurements should be taken prior to scheduled blood collections (if applicable). Measurements should be assessed consistently throughout the study and will be recorded in the source documents and eCRF.

The vital signs measurements obtained prior to dosing on Day 1 will serve as the baseline measurements for clinical assessment.

Mammogram

Mammograms at Screening will only be required for subjects who are 39 years of age or older and have not had one performed within 3 months prior to the time of entry into Screening. If a subject's mammogram results are incomplete (BI-RADS 0) and need to be repeated, the AbbVie TA Scientific Director does not need to be contacted for approval prior to conducting the repeat mammogram or other mode of imaging (e.g., ultrasound, spot compression). If these results meet entry requirements, subject would be allowed to continue in Screening.

If the repeat mammogram or other breast imaging results indicate further testing is required (e.g., breast biopsy) to rule out any potential exclusionary findings, the subject is not eligible for the study. Any further imaging or testing will be performed outside of the protocol and should follow standard of care.

Mammograms will be read locally and the local radiologist's interpretation will be used to determine if a subject meets eligibility criteria. Subjects with normal or benign findings or BI-RADS Classifications 1 or 2 (via mammogram or other mode of imaging) as outlined in Appendix D will be eligible for study drug dosing on Day 1. Subjects with an

abnormal mammogram or BI-RADS 3, 4, 5, or 6 will not be eligible for the study. Subjects should continue with recommended mammography testing outside of the protocol per local guidelines and standard of care during the study.

TVU

The TVU will be performed by the site, affiliated Radiology Department or ultrasound facility per the acquisition guidelines provide by the Central Imaging Core Lab (central reader). The ultrasonographer or designee for each investigative site should submit electronically the subject's TVU imaging data to the central reader within 3 business days following collection in order to determine eligibility for participation in this study and for subject evaluation during the course of the study.

TVUs will be assessed both locally and by a central reader. The TVU performed during the Screening Period will assess subject eligibility and establish baseline findings. The Central Imaging vendor will issue a qualification form documenting the presence or absence of protocol-defined exclusionary pathology during Screening. Subject eligibility will be based on the central reader's or AbbVie TA Scientific Director/MD's assessment, which will override the local radiologist's assessment. If a repeat TVU is performed per protocol, data reported from both procedures may be taken into the consideration by the AbbVie TA Scientific Director/MD when assessing eligibility. The TVU data from the central imaging vendor will be used for analysis and for subject management.

The Investigator should consult the local ultrasound report (or images if the report is not available) in order to make any safety related judgments concerning the subject. In this case, the local ultrasound reports will be maintained in the subject's source documents and copies may be collected upon request by the Sponsor. Data from the local ultrasound report will not be reported in the eCRF unless associated with an adverse event.

The Screening TVU should be performed during the subject's early proliferative phase of the menstrual cycle (approximately Days 4 – 8 of the cycle). The Screening TVU may be repeated per protocol (e.g., ovarian cyst criteria) or as clinically appropriate.

During the Treatment Period, a TVU will also be performed at Month 12 and Month 24 or the Premature Discontinuation (PD) visit (for subjects who prematurely discontinue at the time of or after their Treatment Month 6 visit, unless the subject had a study TVU within approximately 1 month prior to the PD visit). Sites will receive reports from the central reader detailing the results of the TVU performed for these visits.

The TVU for the Month 12 and Month 24 visit may be performed within approximately ± 15 days of the scheduled corresponding visit to allow for the evaluation of results. Per Investigator review of the report from the central reader, subjects with clinically significant ovarian, endometrial or other abnormal findings in the opinion of the Investigator will require a repeat TVU, saline infusion sonography (SIS) or office hysteroscopy. The repeat TVU will be submitted to the central reader; the SIS or office hysteroscopy will be read locally, with results recorded in the source and eCRF. If in the Investigator's clinical judgment, the clinically significant findings persist on the repeat procedure and would preclude the subject from continuing in the Treatment Period due to safety reasons, the subject will be discontinued from the Treatment Period (Section 5.4). If a repeat TVU is performed per protocol, data reported from both procedures may be taken into the consideration by the Investigator/AbbVie TA Scientific Director/MD when assessing.

Assessments to be completed by the central imaging vendor include, but are not limited to:

- endometrial thickness (double layer, mm)
- other clinically relevant endometrial findings
- presence/size/location of uterine fibroids
- presence/size/appearance (simple versus complex) of ovarian cysts
- presence/size/appearance of endometriomas.

An unscheduled (elective) TVU (with a local read) may also be performed as clinically indicated for subject evaluation during the course of the study. Information regarding this procedure should be recorded in the source documents and eCRF.

Bone Mineral Density (DXA Scan)

DXA scans of the lumbar spine, femoral neck and total hip will be performed throughout the study as indicated in Appendix C, by qualified technologists/radiologists at the site or affiliated imaging facility utilizing GE Lunar or Hologic equipment and per the acquisition guidelines provided by the central imaging vendor selected for the study. The DXA technologist/radiologist or designee for each investigative site should electronically submit the subject's DXA images to the central imaging vendor for review and analysis within 3 business days following acquisition. Subject eligibility and treatment management will be made based on results issued by the central imaging vendor. Sites will receive reports from the central imaging vendor detailing the results (including BMD measurements and Z- and T-scores of the DXA scans performed. Instructions on calibration and standardization of instruments and any additional required information will be specified in a manual from the central imaging vendor that will be provided to all study sites. Site training and qualifications, including assessment of instruments, will be evaluated/approved by the central imaging vendor, ideally prior to screening the first subject.

DXA Scan Performed in the Screening Period

The DXA scan performed during the Screening Period will be used to determine eligibility and will serve as the baseline scan for subject management. Subjects with a Z-score or T-score of < –2.0 at the lumbar spine, total hip **or** femoral neck on the screening DXA scan will not be eligible for enrollment into the study.

DXA Scans Performed in the Treatment Period

DXA scans are required to be performed for all subjects during the Treatment Period at Months 6, 12, 18, and 24 and will be submitted to the central imaging vendor for review

and analysis. The central imaging vendor will be blinded to the subjects' treatment assignment, but not to the corresponding time point.

The window for performing DXA scans at Treatment Months 6, 12, 18, and 24 is ± 15 days around the respective study visit.

If the results of any post-baseline DXA prior to and including Month 24, as read by the central imaging vendor selected for the study, document either of the following results, the subject must be discontinued from study drug dosing and will enter the Follow-Up Period:

- a Z-score (for subjects < 40 years of age at the time of the Screening DXA) or T-score (for subjects ≥ 40 years of age at the time of the Screening DXA) of < –2.5 in the lumbar spine, total hip or femoral neck, the subject OR
- a BMD decrease from baseline of > 8% in the lumbar spine, total hip or femoral neck.

A BMD decrease at any anatomic region (lumbar spine, total hip or femoral neck) that results in discontinuation from the study should be reported as an adverse event (Section 6.1.1).

DXA Scans Performed for Subjects Who Prematurely Discontinue in the Treatment Period

DXA scans are required to be performed as part of the Premature Discontinuation visit as follows:

- Subjects who discontinue prior to the Treatment Month 6 visit only if the reason for premature discontinuation is due to the occurrence of a fracture or any newly diagnosed bone condition
- Subjects who discontinue at the time of or after the Treatment Month 6 visit.

However, if a subject is being discontinued from the study due to a Z-score or T-score of < –2.5 in any region, or BMD decrease from baseline of > 8% in any region, additional

DXA scans do not need to be performed as a part of the Premature Discontinuation visit procedures. In these circumstances, the subject would enter the Follow-Up Period and continue with required BMD evaluations.

DXA Scans Performed in the Follow-Up Period

DXA scans of the lumbar spine, total hip, and femoral neck will be obtained at Follow-Up Months 6 and/or 12 for those subjects whose follow-up period visits occur prior to the study conclusion (i.e., approximately 30 days after the last completed Treatment Period visit).

Endometrial Biopsy

Endometrial biopsies will be performed during the Screening and Treatment Periods, as indicated in Appendix C. Instructions on endometrial biopsy collection, processing and shipping procedures will be provided by the central laboratory selected for this study. All central laboratory pathologists will be blinded to the subjects' treatment group assignments. Endometrial biopsies will be independently read by two qualified central laboratory pathologists. If the results are discrepant, the biopsy will be read by a third central laboratory pathologist to facilitate resolution and the worst case reading (of all three reads) will be taken as the final diagnosis. A final pathology report containing the final diagnosis from the central laboratory will be issued to the Investigator in all cases.

Prior to performing the endometrial biopsy, a negative urine pregnancy result must be obtained on the day of the procedure. The Investigator should write a brief procedure note in the source documentation noting the depth of placement of the Pipelle during the procedure. Pre-medication for the endometrial biopsy procedure is allowable. At the investigator's discretion, misoprostol for cervical dilation is allowable. In addition, lidocaine may be used as local anesthesia on the cervix. Any medications used for the procedure should be recorded in source documents and on the appropriate eCRF. If an endometrial biopsy cannot be performed because of anatomical reasons, the AbbVie TA

Scientific Director should be contacted who will consult with AbbVie TA MD for further guidance.

If the endometrial biopsy is performed on the same day as the Pap test or TVU, the endometrial biopsy should be performed after the Pap test and TVU.

Biopsy results from the central laboratory must be obtained and reviewed by the Investigator to ensure eligibility criteria are met before the subject can be randomized on Day 1. In case of an insufficient sample the biopsy should be repeated. Subjects must have an adequate endometrial biopsy with results documenting no significant endometrial pathology in order to be eligible for study enrollment on Day 1. However, if the repeat sample is deemed insufficient by the central laboratory, the AbbVie Scientific Director should be contacted who will consult with AbbVie TA MD and provide recommendation regarding eligibility.

On the Screening endometrial biopsy, if a clinically significant abnormal finding such as endometrial hyperplasia (with or without atypia) or endometrial cancer is reported, subjects will not be eligible for enrollment into the study. If the Investigator determines that an abnormal finding (e.g., endometritis) can be treated outside of the protocol, a repeat biopsy can be performed after treatment at the Investigator's discretion. The results of the repeat biopsy will determine if the subject may remain in Screening. The repeat biopsy must meet eligibility criteria prior to study enrollment.

The endometrial biopsies required during the Treatment period may be performed within approximately ± 15 days around the scheduled study visit. At Treatment Month 12, subjects with significant endometrial pathology (e.g., acute or chronic endometritis, endometrial hyperplasia, endometrial cancer) will not be allowed to continue in the Treatment Period and will be prematurely discontinued. Treatment of subjects with endometrial pathology should be managed according to the Investigator's clinical judgment and local standard of care, and should be documented appropriately in source documents and eCRFs. Clinically significant changes from baseline should be documented as an adverse event.

For subjects with an insufficient endometrial biopsy at either Treatment Period Month 12 or Month 24 whose concurrent TVU indicates an endometrial thickness > 4 mm, a repeat biopsy must be performed. If upon repeat, a sample cannot be obtained or remains insufficient, the AbbVie Scientific Director should be contacted who will consult with AbbVie TA MD.

Pap Test

Pap test will be performed on all subjects at the visits listed in Appendix C. Pap Tests will be performed using the Thin Prep® Pap Test™ provided and analyzed by the central laboratory selected for the study. If the subject is experiencing uterine bleeding that precludes the performance of the Pap test, this procedure should be performed as soon as possible after the uterine bleeding has ended. In the case of an unsatisfactory sample, the Pap test can be repeated. However, in order to be enrolled in the study, the Screening Pap test must contain adequate endocervical cells and show no evidence of malignancy or pre-malignant changes prior to study drug dosing on Day 1.

Subjects with following finding will be eligible for enrollment into the study:

- ASC-US (atypical squamous cells of undetermined significance) who are negative for high risk human papillomavirus (HPV)

Subjects ≥ 25 years of age (at the time the Pap Test is performed) with the following diagnoses will need to undergo additional evaluation with colposcopy and cervical biopsy:

- ASC-US with high risk HPV
- Low-grade squamous intraepithelial lesion (LSIL) (unless a colposcopy with cervical biopsy has been performed within the prior year and results are available for review).

Those subjects with a histology finding of CIN 1 or less (from the colposcopy and cervical biopsy) are eligible for the study.

Subjects ≤ 24 years of age (at the time the Pap test is performed) with the above diagnoses do not require additional evaluation with colposcopy and cervical biopsy and are eligible for the study.

Subjects with the following cytology screening/colposcopy results are not eligible for enrollment into the study:

- atypical squamous cells cannot exclude HSIL (ASC-H),
- high-grade intraepithelial lesion (HSIL),
- atypical glandular cells (AGC) or epithelial cell abnormality,
- cervical intraepithelial neoplasia grade 2 (CIN 2) (on cervical biopsy),
- cervical intraepithelial neoplasia grade 3 (CIN 3) (on cervical biopsy).

For any atypical finding that can be treated, please contact the AbbVie TA Scientific Director who will consult with AbbVie TA MD to determine if the subject may remain in screening and can be eligible for enrollment.

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 4, at the time points indicated in Appendix C.

Table 4. Clinical Laboratory Tests

Hematology	Clinical Chemistry (After Minimum 8-Hour Fast)	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands (if indicated) Lymphocytes Monocytes Basophils (if indicated) Eosinophils (if indicated) Platelet count (estimate not acceptable) Mean Cell Volume of RBC (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC)	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen (BUN) Serum creatinine Glucose Calcium Total protein Albumin Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Vitamin D	Specific gravity Ketones Protein Blood Glucose pH
		Lipid Panel (After Minimum 8-Hour Fast)
		Low-density Lipoprotein (LDL) cholesterol High-density Lipoprotein (HDL) cholesterol Total cholesterol Triglycerides
Pregnancy Test		**Endocrine**
Serum pregnancy		Follicle-stimulating hormone (FSH) Reflexive Thyroid Stimulating Hormone (TSH)

Laboratory samples indicated in Table 4 will be assessed using the certified central laboratory selected for the study and these data will be used for data analysis. The central laboratory will provide instructions regarding the collection (including any fasting requirements), processing and shipping of samples. Blood draws should be performed after efficacy assessments, vital signs and ECG recordings are conducted at a visit. Clinical chemistry panel samples should be obtained in the morning following an overnight fast (minimum of 8 hours); however, there may be circumstances when a sample is obtained later in the day and/or not under fasting conditions. If a sample was obtained after less than 8 hours of fasting, the lab requisition should be marked to indicate that the sample was obtained under non-fasting conditions. All clinical laboratory samples will be shipped to the central laboratory.

The laboratory results will be provided by the central laboratory to the investigative site where they will be reviewed, signed and dated by the Investigator. For any value outside of the reference range, the Investigator will review and indicate on the report if the result is clinically significant or not clinically significant. The Investigator will evaluate clinically significant laboratory values per standard of care which may include repeating the test to verify the out-of-range value. Clinically significant laboratory abnormalities post study drug dosing are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention and/or if the Investigator considers them to be adverse events (Section 6.1.1).

All screening laboratory results must be reviewed prior to enrollment, including any repeated test results. Screening laboratory tests may be repeated one time prior to Day 1, however, results must satisfy entry criteria prior to enrollment. Subjects will not be enrolled on Day 1 if Screening laboratory results do not meet entry criteria or are assessed as clinically significant by the Investigator. The laboratory test results obtained from the Day 1 pre-dose samples will serve as the baseline for clinical assessment.

Lipid Panel

Serum lipids consist of LDL cholesterol, HDL cholesterol, triglycerides and total cholesterol; non-HDL cholesterol and lipid ratios will also be calculated, but will not be reported to the investigative site.

The lipid panel samples should be obtained in the morning following an overnight fast (minimum of 8 hours); however, there may be circumstances when a sample is obtained later in the day and/or not under fasting conditions. If a sample was obtained after less than 8 hours of fasting, the lab requisition should be marked to indicate that the sample was obtained under non-fasting conditions.

Endocrine Testing

The endocrine testing for the study consists of the following analytes: serum FSH and reflexive TSH. Reflexive TSH will be obtained at Screening only.

Optional Testing for Gonorrhea and Chlamydia

Gonorrhea and chlamydia testing can be ordered at the Investigator's discretion during the Screening and Treatment Periods, to test for active gonorrhea or chlamydia prior to performing the endometrial biopsy or Pap test. These samples will be sent to the central laboratory for analysis. If the Investigator determines that an abnormal test result can be treated, treatment will be outside of the protocol. Follow-up chlamydia/gonorrhea testing (per instructions from the central lab) can be performed after treatment at the Investigator's discretion.

Serology Screening for Hepatitis and HIV

Samples will be tested for HAV-IgM, HBsAg, HCV Ab, HIV Ag/anti-HIV Ab by the central laboratory for all subjects during the Screening Period. If any of these tests are positive or reactive, the subject is excluded from study participation. Borderline hepatitis test results should be repeated.

The results of the HIV Ag/anti-HIV Ab testing will be retained confidentially by the study site.

Electronic Daily Diary (e-Diary)

An electronic patient-recorded outcomes device (e-Diary) will be provided to all subjects during Screening, and subjects will record daily entries through Treatment Month 6. The e-Diary contains training information for the subject and/or site staff will provide training on the required entries in the e-Diary. Subjects will also be instructed to complete the diary at approximately the same time(s) every day from Screening through Month 6 of the Treatment Period, including prior to study visits as applicable. The e-Diary will also remind subjects about consistent use of acceptable forms of non-hormonal contraception.

Site staff should review subject e-Diary data periodically beginning at Screening through Treatment Month 6, as well as at every study visit, to ensure subject comprehension and completion. Subjects who are screen failures will be instructed to return the e-Diary device to the site. All subjects will be instructed to return the e-Diary device to the site at

the Treatment Month 6 study visit or at the Premature Discontinuation visit (if prior to Treatment Month 6).

Subjects will use the e-Diary to record assessments of DYS or NMPP, dyspareunia, menstrual period, uterine bleeding, Daily Diary endometriosis-associated pain score via NRS, as well as the use of protocol-allowed rescue analgesic medications for endometriosis-associated pain. Scores from applicable daily assessments collected during Screening will be used to evaluate subject eligibility for the study prior to Open Label Run-In period on Day 1 E-Diary assessments will continue to be completed daily through Month 6 of the Treatment Period or until a subject prematurely discontinues from the Treatment Period (if they discontinue prior to Treatment Month 6).

Subject responses to the Daily Diary endometriosis-associated pain score via NRS will be used at Treatment Month 3 and Month 6 to determine subject status of efficacy responder and incomplete efficacy responder.

Based on the subject's response to the question "Did you have your period in the last 24 hours?" in the daily e-Diary, the subject will be asked to assess either their dysmenorrhea or non-menstrual pelvic pain as follows:

Dysmenorrhea (DYS)

Subjects will be asked to assess their DYS and its impact on their daily activities. Subjects will be prompted to "Choose the item that best describes your pain during the last 24 hours when you had your period."

None	No discomfort.
Mild	Mild discomfort but I was easily able to do the things I usually do.
Moderate	Moderate discomfort or pain. I had some difficulty doing the things I usually do.
Severe	Severe pain. I had great difficulty doing the things I usually do.

Non-Menstrual Pelvic Pain (NMPP)

Subjects will be asked to assess their NMPP and its impact on their daily activities. Subjects will be prompted to "Choose the item that best describes your pain during the last 24 hours without your period."

None	No discomfort.
Mild	Mild discomfort but I was easily able to do the things I usually do.
Moderate	Moderate discomfort or pain. I had some difficulty doing the things I usually do.
Severe	Severe pain. I had great difficulty doing the things I usually do.

Dyspareunia

Subjects will be asked to assess their dyspareunia (described as 'pain during sexual intercourse'). Subjects will be prompted to "Choose the item that best describes your pain during sexual intercourse during the last 24 hours."

Not applicable	I was not sexually active for reasons other than my endometriosis or did not have sexual intercourse.
None	No discomfort during sexual intercourse.
Mild	I was able to tolerate the discomfort during sexual intercourse.
Moderate	Intercourse was interrupted due to pain.
Severe	I avoided sexual intercourse because of pain.

Uterine Bleeding

Subjects will be prompted to indicate if they had "Did you have any uterine bleeding in the last 24 hours?" For subjects who answer yes, the subject will then document the intensity of the bleeding as follows:

Spotting	A light amount of bleeding noted, no protection or panty shield only.
Light	1 to 2 regular tampons or pads required in 24 hours.
Medium	3 to 4 regular tampons or pads required in 24 hours.
Heavy	More than 4 tampons or pads required in 24 hours.

Daily Diary Endometriosis-Associated Pain Score via Numeric Rating Scale (NRS)

Beginning at Screening, subjects will complete the Daily Diary endometriosis-associated pain score via NRS through Month 6. Subjects will assess in the e-Diary their endometriosis-associated pain during the past 24 hours on a scale of 0 – 10, with 0 = no pain and 10 = worst pain ever.

Rescue Analgesic Use for Endometriosis-Associated Pain

Subjects will record the use of protocol-allowed rescue analgesic medications (Section 5.2.3.4) taken for endometriosis-associated pain on a daily basis using the e-Diary during the Screening Period and through Treatment Month 6. Subjects will report whether they have taken pain medication and document the total number of pills taken within each class (NSAIDs and/or opioids) of protocol-allowed rescue analgesic during the last 24-hour period.

The use of protocol-allowed rescue analgesic medications taken during Treatment Months 7 – 24 will be recorded in the subjects' source documents and eCRF.

Patient Reported Outcomes (PRO) and Outcomes Rating Scales

Prior to the start of the study, instructions and training for study site staff administering these rating scales will be provided by AbbVie and/or its designee. The following questionnaires will be completed by the subjects and/or the Investigator or site staff, as appropriate at the time points indicated in Appendix C and should be administered prior to any other study procedures being performed at that visit. Subjects and site staff will be asked to record their responses either electronically and/or directly onto paper questionnaires (which will then be entered into the eCRF).

Overall Endometriosis-Associated Pain (7-Day Recall)

Beginning at Day 1 of the Treatment Period and at all monthly visits during the Treatment Period (on-site and telephone contacts), site staff will administer the overall endometriosis-associated pain questionnaire (Appendix E) (11-point NRS) assessing

overall endometriosis-associated pain over a 7-day recall period. Site staff will ask subjects to assess their endometriosis-associated pain on a scale of 0 – 10, with 0 = no pain and 10 = worst pain ever. Site staff will record the subject's response electronically via a tablet device.

Endometriosis Health Profile-30 (EHP-30)[9]

The EHP-30 is a disease-specific self-administered questionnaire used to measure health related quality of life in women with endometriosis. The EHP-30 is composed of two parts: a core questionnaire containing 5 scales that are applicable to all women with endometriosis and a modular part containing 6 scales which do not necessarily apply to all women with endometriosis. This study will employ the Core EHP-30 and modular Section C-Sexual Relationships (Part 2). Subjects will complete the EHP-30 electronically via a tablet device.

EuroQol-5D 5 level (EQ-5D-5L™)[10,11]

The self-administered EQ-5D-5L is a standardized measure comprised of 5 questions, measuring 5 dimensions of health status (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Subjects will be asked to select a response to each category that best describes their current health. The EQ-5D-5L also contains a visual analogue scale that provides quantitative measure of health as judged by the individual respondents. Subjects will be asked to rate their current health on a scale of 0 – 100. Subjects will complete the EQ-5D-5L electronically via a tablet device.

Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)[12]

The WPAI:SHP questionnaire is a standardized, self-administered questionnaire about work and activity impairment due to a specific health problem. The WPAI-SHP will be completed by subjects electronically via a tablet device, and the SHP referenced is endometriosis-associated pain.

PROMIS Fatigue Short Form 6a[13]

The PROMIS Fatigue Short Form 6a is self-administered and composed of 6 questions to evaluate fatigue. Subjects will complete this questionnaire on an electronic tablet device.

Patient Global Impression of Change (PGIC)

The Patient Global Impression of Change (Appendix F) questionnaire evaluates the change in the subject's endometriosis-related pain since initiation of study drug. The subject selects one of seven responses using a tablet device: very much improved, much improved, minimally improved, not changed, minimally worse, much worse or very much worse.

Health Endometriosis Treatment Satisfaction Questionnaire (ETSQ)[14]

This 6-item measure was developed to assess patient-reported satisfaction with effects on endometriosis pain, dysmenorrhea, dyspareunia, amount of bleeding tolerability and overall treatment satisfaction. The ETSQ has a 7 point response scale. Subject will complete this questionnaire on an electronic tablet device.

Health Care Resource Utilization (HCRU)

The Health Care Resource Utilization questionnaire captures subject visits to non-study Health Care Practitioners at Day 1 and during the Treatment Period. At all study visits (on-site and telephone call) subjects will be asked to provide information on any visits to non-study Health Care Practitioners for non-study health visits since their last scheduled monthly study visit (or the prior month for the Day 1 assessment). The subject's responses will be recorded on the HCRU hard-copy worksheet by the site staff.

Additional Questionnaires

BMD Risk Factor Assessment Questionnaires (Appendix G)

Information will be obtained at study visits as outlined in Appendix C to help identify risk factors potentially associated with changes in BMD. Subjects will be asked about

modifiable and non-modifiable risk factors, e.g., smoking and alcohol use, physical activity, and dietary intake of calcium. Information about physical activity will be collected via the International Physical Activity Questionnaire Short Last 7 Days Self-Administered format (IPAQ).[15] As applicable per questionnaire, site staff will elicit subject responses and record appropriately or, subjects will be asked to enter their responses electronically.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The Screening-Baseline C-SSRS questionnaire will be administered by site staff at Screening and on Day 1. The C-SSRS Since Last Visit questionnaire should be administered by site staff during the Treatment Period as indicated in Appendix C.

Post-Treatment Assessment of Menstruation

Subjects will be asked about occurrence of post-treatment menses in the Follow-Up Period, as outlined in Appendix C. Site staff will ask subjects if they have had a menstrual period since discontinuation of study drug and record subjects' responses directly onto the paper questionnaire (which will then be entered into the eCRF). If the subject indicates she has not had a post-treatment menses, site staff will continue to assess menstruation and repeat the questionnaire at subsequent follow-up visits, as applicable. The date when menses started since discontinuation of study drug will be documented in the source documents and eCRFs.

Assignment of Subject Numbers

The site will contact IRT during the Washout or Screening Period to obtain a subject (Screening) number after the subject has signed the informed consent. Consecutive and

unique subject numbers within each site will be assigned. The same subject number will be used to identify the subject throughout the study (Screening, Treatment and Follow-Up Periods). If the subject is not enrolled into the study on Day 1, the reason for screen failure will be documented in the eCRF and the site will register the subject as a screen failure in IRT.

5.3.1.2 Collection and Handling of Pharmacodynamic Variables

A single blood sample will be collected at each timepoint as indicated in Appendix C to be used for the analysis of estradiol and potentially for additional testing (e.g., re-testing of hormone levels with an alternative methodology or for testing and potential validation of exploratory biomarkers for endometriosis). The blood samples for assay of estradiol will be collected by venipuncture in one 6 mL evacuated collection tube without anticoagulant (red cap, no gel separators to be used). Sufficient blood volume will be collected to provide approximately 3 mL serum from each sample. Refer to the study specific laboratory manual for detailed instructions on sample collection, processing and shipment.

The Day 1 and Treatment Months 3 and 6 samples will be obtained pre-dose; samples collected at all other visits can be drawn at any time during the visit. The date and time of collection, as well as the dosing times of the two prior doses of study drug will be recorded in the subject's source documents and the eCRF.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for assay of elagolix and norethindrone (PK samples) will be collected by venipuncture into 4 mL evacuated K_2-ethylenediaminetetraacetic acid (K_2EDTA)-containing collection tubes at the times indicated in Appendix C. Sufficient blood will be collected to provide approximately 2 mL plasma from each sample. Refer to the study specific laboratory manual for detailed instructions on sample collection, processing and shipment.

At Month 3 and Month 6, samples will be collected before the drug dispensation or administration of drug at the site (the first dose of study drug from the newly assigned study drug kit will be administered at the site at these visits). At all other designated visits, samples will be collected regardless of the time of last dose. A total of 6 blood samples for pharmacokinetic analysis are planned to be collected per subject during study participation. The date and time of collection, as well as the dosing times of the two prior doses of study drug, will be recorded in the source and the eCRF.

5.3.2.2 Measurement Methods

Plasma concentrations of elagolix and norethindrone and serum concentrations of estradiol will be determined using validated methods by the Drug Analysis Department at AbbVie. Plasma or serum concentrations of other possible metabolites may be determined with validated or non-validated methods.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variables

The co-primary efficacy endpoints will be the proportion of responders (Figure 1, treatment Group B versus treatment Group C) at Month 6 based upon the mutually-exclusive scales for daily assessment of DYS and NMPP measured by the 4-point Endometriosis Daily Pain Impact Diary. Use of protocol specific analgesic medication for endometriosis-associated pain collected in the daily e-Diary will also be included in the responder definition.

5.3.3.2 Secondary Variables

The following efficacy variables will be collected in the daily e-Diary through Treatment Month 6 and will be summarized:

- DYS
- NMPP
- Dyspareunia

- Daily Diary endometriosis-associated pain score via NRS
- Rescue analgesic medication use

In addition, the following efficacy variables will be collected and summarized:

- PGIC
- Overall Endometriosis-Associated Pain via NRS (7-day recall)
- Patient reported outcome (PRO) and Outcomes Rating Scales questionnaires

5.3.4 Safety Variables

BMD Assessments:

BMD assessments will be summarized. Modifiable and non-modifiable risk factors will be assessed as they relate to baseline BMD and changes in BMD over time, including: smoking and alcohol use, physical activity (IPAQ), previous use of calcium and vitamin D, prior medications, race, age, height and weight (BMI), family history of fracture and family history of osteoporosis.

Other Safety Assessments:

Safety evaluations will also include physical examinations, AEs and concomitant medications, clinical laboratory tests and vital sign measurements. Endometrial health will be assessed via TVU and biopsy.

5.3.5 Pharmacodynamic Variables

Concentrations of estradiol will be obtained at designated visits throughout the study. Additional pharmacodynamic parameters may be calculated if useful in the interpretation of the data. Estradiol data may be combined with data from other studies and may be used for exposure-response analysis.

5.3.6 Pharmacokinetic Variables

Plasma concentrations of elagolix and norethindrone will be listed for each subject by visit. Elagolix and norethindrone exposures will be summarized. Elagolix pharmacokinetic data may be combined with data from other studies to conduct population pharmacokinetic analysis and may be used in exposure-response analysis.

5.4 Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a subject from the study at any time if the Investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. Subjects who withdraw from the study will not be replaced unless it is mutually agreed upon, in writing, by the Investigator and AbbVie. Subjects will be withdrawn from the study drug treatment and or study if any of the following occur:

- The subject decides to withdraw consent for any reason
- The Investigator believes it is in the best interest of the subject
- Clinically significant deterioration of the subject's medical status as determined by the Investigator
- The subject becomes pregnant or subject has a positive serum pregnancy test
- The subject has ALT or AST elevation > 5 times the upper limit of normal prior to Month 24, confirmed upon repeat testing
- The subject develops clinically significant gynecological findings or condition on either the TVU (confirmed by repeat TVU and/or SIS and/or office hysteroscopy) or endometrial biopsy that in the opinion of the Investigator or AbbVie TA MD/Scientific Director would preclude the subject from continuing in the Treatment Period due to safety reasons
- The results of any post-baseline DXA prior to Month 24 document a Z-score (for subjects < 40 years of age) or T-score (for subjects ≥ 40 years of age) < –2.5 in the lumbar spine, total hip or femoral neck OR a BMD decrease from baseline of > 8% in the lumbar spine, total hip or femoral neck

- The subject will require ongoing use of prohibited medications to manage or treat her endometriosis or endometriosis-associated pain in the opinion of the Investigator or AbbVie TA MD/Scientific Director
- The subject requires use of prohibited medications to manage or treat bone mineral density changes during the Treatment Period as described in Section 5.2.3.3. Subject continuation in the Follow-Up Period is at the discretion of the AbbVie TA MD/Scientific Director.
- The subject requires or elects surgical intervention for treatment of endometriosis or uterine bleeding (e.g., laparoscopy, hysterectomy, ovarian cystectomy)
- In the Investigator's opinion, the subject is unable or unwilling to comply with study-related assessments and procedures, including completion of the e-Diary
- Any other medical reason that AbbVie or the Investigator deems appropriate.

5.4.1 Discontinuation of Individual Subjects

In the event that a subject withdraws or is prematurely discontinued from study drug treatment, the subject should complete the Premature Discontinuation Visit as soon as possible (preferably within 2 – 7 days after last dose of study drug, if possible) and undergo study procedures as outlined in Appendix C. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities the Investigator determines are necessary to treat the subject's condition. The reason(s) for the discontinuation from the Treatment Period will be recorded. Subjects who prematurely discontinue at the time of or after the Month 6 visit during the Treatment Period, or prematurely discontinue due to the occurrence of a fracture or any newly diagnosed bone condition are expected to enter the Follow-Up Period for up to 12 months unless discontinuing due to pregnancy.

If a subject becomes pregnant during the Treatment or within 30 days of the last dose of study drug, no additional study procedures, except an ultrasound will be conducted. Refer to Section 6.1.4 for instructions on reporting of a pregnancy to the Sponsor and the required follow-up on the subject and fetus/infant.

If a subject requires or elects surgery (e.g., laparoscopy, hysterectomy, ovarian cystectomy) for the management of her endometriosis during the Treatment Period, study drug should be discontinued and the Premature Discontinuation visit should be completed prior to surgery, if possible.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is clinically significant (as determined by the Investigator), the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

If a subject is being discontinued from the study prior to the completion of Treatment Month 6, TVU, Pap test, or endometrial biopsy does not need to be performed.

DXA scans are needed if the reason for premature discontinuation is due to the occurrence of a fracture or any newly diagnosed bone condition.

In addition, if a subject is being discontinued from the study due to a documented Z-score or T-score result of < –2.5, or a BMD decrease of > 8% from baseline, an additional DXA scan does not need to be performed as a part of the Premature Discontinuation visit procedures.

Upon discontinuation from the Treatment Period, all used and unused study drug containers and e-Diaries should be returned to the study site.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately

notify the Investigator by telephone and subsequently provide written instructions for study termination.

The following procedures for study discontinuation will be followed:

- If the Sponsor has decided to prematurely discontinue the study, the Sponsor will promptly notify the Investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- The Investigator must promptly notify the IRB/IEC and give detailed reasons for the discontinuation.
- The Investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of the treatment regimen, if applicable, by other appropriate regimens.

5.5 Treatments

5.5.1 Treatments Administered

All subjects will be administered elagolix 150 mg QD at Day 1 through Treatment Month 3. Subjects will be administered the following open-label treatment regimen for 3 months as indicated in Table 5:

Table 5. Treatments Administered (Day 1 – Month 3)

	Investigational Product	
Treatment Group	**Dosing Time**	**Elagolix 150 mg Tablets QD**
Elagolix 150 mg QD	AM	1
	PM	0

Based on the efficacy responder status as determined at the Treatment Month 3 Visit each subject will be assigned by the IRT to one of the following treatment groups:

- Elagolix 150 mg QD. This includes subjects who are efficacy responders at Month 3 (Group A), and subjects who are incomplete efficacy responders and randomized to receive 150 mg QD (Group B)

- Elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD. This includes subjects who are incomplete efficacy responders at Month 3 and randomized to receive 200 mg BID plus E2/NETA 1/0.5 mg QD (Group C)

At the Treatment Month 6 Visit, the efficacy responder status will again be reassessed in the same blinded manner as at Month 3. Each subject will be assigned by the IRT to one of the following treatment groups:

- Elagolix 150 mg QD. This includes:
  - Subjects who are efficacy responders at Treatment Month 3 and continue treatment through Month 24 (Group A), and
  - Subjects who are incomplete efficacy responders at Treatment Month 3, randomized to receive 150 mg QD and are efficacy responders at Treatment Month 6 and continue treatment through Month 24 (Group E)
- Elagolix 200 mg BID plus E2/NETA. This includes
  - subjects who are incomplete efficacy responders at Treatment Month 3, randomized to receive 200 mg BID plus E2/NETA 1/0.5 mg QD and continue treatment through Month 24 (Group C), and
  - subjects who are incomplete efficacy responders to elagolix 150 mg QD at Treatment Month 3, randomized to elagolix 150 mg QD treatment group and are incomplete efficacy responders at Treatment Month 6, and dose increased to elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD through Month 24 (Group D).

The treatment administration for treatment Months 4 through 24 is presented in Table 6.

Table 6. Treatments Administered (Month 4 – Month 24)

		Investigational Product					
Treatment Group	**Dosing Time**	**E2/NETA Capsules**	**E2/NETA Placebo Capsules**	**Elagolix 150 mg Tablets**	**Elagolix 150 mg Placebo Tablets**	**Elagolix 200 mg Tablets**	**Elagolix 200 mg Placebo Tablets**
Elagolix 150 mg QD plus Placebo to match Elagolix 200 mg BID and E2/NETA QD	AM	0	1	1	0	0	1
	PM	0	0	0	0	0	1
Elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD plus Placebo to match Elagolix 150 mg	AM	1	0	0	1	1	0
	PM	0	0	0	0	1	0

The elagolix study drug, consisting of open-label elagolix 150 mg (Day 1 – Treatment Month 3 only), will be supplied in a carton. The subject will take the elagolix dose orally in the morning at the study site on Day 1. Subjects will be instructed to thereafter self-administer their study drug throughout the 3 month Open-Label Run-In Period. After Treatment Month 3, elagolix study drug consisting of elagolix 150 mg or placebo, and elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD or placebo will be supplied in a carton.

A 1-month (28-day) supply of each study drug (plus 1 week additional supply) will be dispensed at the Day 1 visit and at each subsequent monthly study visit up to Month 5 of the Treatment Period. For Treatment Month Visits 6 – 10, a 2 month supply (two 28-day kits, plus 2 weeks additional supply) will be dispensed at each on-site monthly visit (i.e., Months 6, 8, and 10) to last until the next scheduled study visit. Likewise, for Treatment Months 13 – 24, a 3 month supply will be dispensed at each on-site visit (Months 12, 15, 18, and 21), with enough to supply subjects until the next scheduled on-site visit.

From Treatment Month 3 through Treatment Month 24, study drug will be taken orally twice daily. A morning dose of 1 tablet elagolix 150 mg or placebo, 1 tablet elagolix 200 mg or placebo, and 1 capsule of E2/NETA or placebo, and an evening dose of 1 capsule elagolix 200 mg or placebo should be taken each day approximately 12 hours apart. Study drug should be taken with approximately 8 oz (240 mL) of water without regard to food. Study drug should be taken at approximately the same time each morning and evening to promote compliance.

If the subject forgets to take the morning dose during treatment Months 1 – 3, the subject should be instructed to take the morning dose as soon as possible. If the subject forgets to take the morning dose during treatment Months 4 – 24 the subject should be instructed to take the morning dose as soon as possible and take the evening dose as scheduled. If the subject forgets to take the evening dose, she should be instructed to take the evening dose as soon as possible; if the subject misses the evening dose completely (until the next morning), the subject should only take the next morning dose.

On days when the subject visits the study site for the scheduled visits, she should take her morning dose at home, prior to the visit. For study visits at Treatment Months 3 and 6, the first doses from the newly assigned study drug kit will be administered on-site. The evening dose will be taken from the newly dispensed supply of study drug. Subjects must return all study drug containers at each on-site visit.

5.5.2 Identity of Investigational Products

Information about the drug formulations to be used in this study is presented in Table 7.

Table 7. Identity of Investigational Products

Study Drug	Formulation	Route of Administration	Manufacturer
Elagolix (ABT-620)	150 mg Film coated tablets	Oral	AbbVie
Matching Elagolix (ABT-620) Placebo	Placebo FilmCoated tablets	Oral	AbbVie
E2/NETA*	Estradiol 1 mg/ Norethindrone acetate 0.5 mg Hard Gelatin Capsule	Oral	Novo Nordisk, A/S
Matching (E2/NETA Placebo	Placebo Hard Gelatin Capsule	Oral	AbbVie
Elagolix (ABT-620)	200 mg Film Coated Tablet	Oral	AbbVie
Matching Elagolix (ABT-620) Placebo	Placebo Film Coated Tablet	Oral	AbbVie

* Note: Commercially available as Activella® 1 mg/0.5 mg.

5.5.2.1 Packaging and Labeling

AbbVie will supply open label and blinded study drug in monthly kits (i.e., cartons). For the open label kit, one kit consists of Elagolix 150 mg. Each kit will contain 5 weekly blister cards, with each blister card containing 7 days of study medication; 4 blister cards for the 28 days of drug administration and 1 blister card in case of lost/damaged medication, late visit, etc.

For blinded supplies, subjects will receive two kits:

- One kit of elagolix 150 mg or matching placebo tablet and elagolix 200 mg or matching placebo tablet. The kit will contain morning and evening doses
- One kit of E2/NETA (1 mg/0.5 mg) capsule or matching placebo. The kit will only contain the morning dose.

Each kit will contain 5 weekly blister cards, with each blister card containing 7 days of study medication; 4 blister cards for the 28 days of drug administration and 1 blister card in case of lost/damaged medication, late visit, etc.

The kits will be assigned to a subject via IRT and will encode the appropriate study drug to be dispensed at the subject's corresponding study visit. Each kit will contain a unique kit number.

The kits and blister cards are labeled as per country requirements. All blank spaces on the label will be completed by the site staff prior to dispensing to the subject. Labels must remain affixed to the study drug containers. Adequate supplies of study drug will be provided to each study site automatically via IRT.

5.5.2.2 Storage and Disposition of Study Drug

Elagolix, E2/NETA and respective matching placebo study medication must be stored at controlled room temperature 15°C to 25°C (59° to 77°F).

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie. Returned study drug should not be re-dispensed to the subject.

5.5.3 Method of Assigning Subjects to Treatment Groups

On Study Day 1, all subjects will begin dosing with Elagolix 150 mg QD. The first dose of study drug will be administered at the study site on Day 1 and study drug kits will be dispensed to subjects to continue daily dosing. At the Treatment Month 3 study visit, subjects will be assessed as either an 'efficacy responder' or an 'incomplete efficacy responder' based on responses entered in the e-Diary on the Daily Diary endometriosis-associated pain score via NRS. The status of a subject will be determined in the IRT system and will remain blinded. The Daily Diary endometriosis-associated pain score via

NRS data within the e-Diary system will transfer into IRT on a daily basis with a blinded calculation as follows:

- Efficacy responder: the mean of the responses on the Daily Diary endometriosis-associated pain score via NRS for the 35 days prior to the Treatment Month 3 visit demonstrate ≥ 30% decrease (improvement) from the mean of the responses 35 days prior to the first dose of study drug (Baseline Daily Diary endometriosis-associated pain score via NRS)
- Incomplete efficacy responder: the mean of the responses on the Daily Diary endometriosis-associated pain score via NRS for the 35 days prior to the Treatment Month 3 visit does not demonstrate ≥ 30% decrease (improvement) from the mean of the responses 35 days prior to the first dose of study drug (Baseline Daily Diary endometriosis-associated pain score via NRS)

Following conclusion of the Open-Label Run-In Period, treatment arm assignment for all subjects will become and remain blinded for the remainder of the 24-month Treatment Period. To preserve the blind, at Treatment Months 3 and 6, IRT will be utilized for treatment assignment of all subjects regardless of treatment assignment.

At the Treatment Month 3 visit (i.e., the end of the Open-Label Run-In Period), in a blinded manner, the efficacy response for a subject will be assessed via the Daily Diary endometriosis-associated pain score via NRS. Subjects assessed as "efficacy responders" will continue dosing in Treatment Group A in a blinded manner for the remainder of the Treatment Period. All other subjects (assessed as "incomplete efficacy responders") will be assigned randomly (in an equal ratio) via IRT in a blinded manner to either Treatment Group B or Treatment Group C for 3 months. During the IRT randomization contact session, a unique randomization number and study drug kit number will be assigned by the IRT according to a randomization schedule generated by the Statistics department at AbbVie. However, the randomization number will not be provided to the site and is strictly used within the system for treatment assignment. At the Treatment Month 6 study visit, in a blinded manner, subjects will again be assessed for efficacy response via the Daily Diary endometriosis-associated pain score via NRS in a similar manner as was done

at the Treatment Month 3 visit. All Month 3 "incomplete efficacy responders" that were randomly assigned to be on Treatment Group B who become "efficacy responders" will continue dosing in Treatment Group E in a blinded manner. All other Month 3 'incomplete efficacy responder' subjects on Treatment Group B who are assessed as 'incomplete efficacy responders' at Month 6 will escalate dosing to Treatment Group D. To preserve the blind, at Month 6, IRT will be utilized for treatment assignment of all subjects; however, only Month 3 'incomplete efficacy responder' subjects on Treatment Group B for the additional 12 weeks after Treatment Month 3 will have a chance for dose modification. The subject number assigned via IRT at Washout of Screening does not change throughout the study.

The treatment assignments following the Treatment Month 6 study visit will continue for all subjects for the duration of the Treatment Period in a blinded manner. There will not be further dose adjustments following the Treatment Month 6 visit for any subject.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses used for this study is discussed in Section 5.6.4. Subjects will be assigned or randomized into treatment groups as appropriate described in Section 5.5.1.

Study drug will be administered at the study site on Day 1 and subjects will be instructed thereafter self-administer study drug once a day in the morning with approximately 8 oz (240 mL) of water. The first dose of study drug from the newly dispensed study drug kit(s) will be administered at the study site at Treatment Months 3 and 6. Starting at Treatment Month 3, subjects will be instructed to thereafter self-administer study drug twice a day (once in the morning and once in the evening, approximately 12 hours apart) with approximately 8 oz (240 mL) of water. Subjects must return all study drug containers (cartons and blister cards, used or unused) at the subsequent on-site study visit.

5.5.4.1 Treatment Interruption

AbbVie or the Investigator may request that a subject temporarily discontinue study drug administration, which will be referred to as "treatment interruption." The following are

examples for reasons when the investigator may consider whether a subject should undergo temporary treatment interruption:

- Adverse event that, based on clinical judgment, requires temporary suspension of study drug or prevents a subject from taking study drug
- Due to malfunction of protocol-specified methods of contraception or unprotected intercourse
- After a positive urine pregnancy test while waiting for results of the serum test
- Clinical laboratory findings that require repeating or confirmation of a clinically significant value (e.g., may necessitate discontinuation from the study).

These examples are not all-inclusive; if the Investigator has any questions, these should be directed to the AbbVie TA Scientific Director who will discuss with AbbVie TAMD and provide a recommendation.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

The active elagolix dose will be identical in appearance to its matched placebo; each active E2/NETA dose will be identical in appearance to its matched placebo. The study site personnel and subject will remain blinded to each subject's treatment during the blinded portion of the study (starting at the Treatment Month 3 visit and will continue until the end of the Treatment Period Month 24).

The IRT will provide access to blinded subject treatment information during the blinded portion of the study. AbbVie must be notified before the blind is broken, unless identification of the study drug is required for medical emergency, i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (AbbVie must then be notified within 24 hours after the blind being broken). The date and reason that the blind was broken must be recorded in the source documents and eCRF, as applicable.

5.5.6 Treatment Compliance

The Investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Subjects will be instructed to return all study drug kits (even if empty, unused or damaged) to the study site personnel at on-site study visits throughout the Treatment Period, or Premature Discontinuation visit (if applicable). The study site personnel will assess dosing compliance at on-site visits.

Subjects should be advised of the importance of treatment compliance. Study drug should be taken consistently at approximately the same time in the morning for Day 1 – Treatment Month 3 and the same time in the morning and evening each day for Treatment Months 4 – 24.

5.5.7 Drug Accountability

The study Investigator or designee will verify via direct recording in IRT and/or by signature and date that study drug supplies are received intact and in the correct amounts indicated on the shipping document Clinical Site Shipment Request (CSSR) or similar shipping document. The shipment receipt must be acknowledged in IRT in order to become available for dispensation to subjects. The IRT must also be contacted when any subject completes or discontinues study drug treatment.

The IRT will maintain a current and accurate inventory of all clinical drug supplies, accountability, reconciliation, returns and destruction for each site. The IRT may also include the lot number, kit number, CSSR number, the number of pills/capsules dispensed and the date study drug was dispensed/returned for each subject. In addition to using IRT inventory, an accurate inventory of study drug may also be kept by the site.

An overall accountability of the study drug will be performed and verified by the site monitor via IRT throughout the study and at the study site closeout visit. Throughout the study and upon completion or termination of the study, all original containers will be returned to AbbVie according to instructions from AbbVie.

The study Investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator.

Study drug will be dispensed at the study visits summarized in Appendix C, Study Activities. Returned study drug should not be re-dispensed to the subject.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a Phase 3 study to investigate the long term safety and efficacy of elagolix in management of endometriosis with -associated moderate to severe pain in addition to providing efficacy data on dose adjustment of elagolix in women who are incomplete responders to elagolix 150 mg QD. This 24 month study will determine the impact of 24 months of elagolix 150 mg QD on bone mineral density as well as the long term impact of 200 mg BID and E2/NETA on bone mineral density (as measured by DXA). Additionally the study will evaluate women at risk for greater decreases in DXA based on modifiable risk factors.

5.6.2 Appropriateness of Measurements

The co-primary efficacy endpoints for this trial will be based upon the mutually-exclusive scales for daily assessment of DYS and NMPP measured by the 4-point Endometriosis Daily Pain Impact Diary. Use of protocol allowed rescue analgesic medication for endometriosis-associated pain will be included in the responder definition of the primary endpoints. Additional secondary efficacy measures of DYS and NMPP, dyspareunia, and the PGIC are widely used in endometriosis as assessment tools. In addition to assessment of pain reduction, the effects of treatment can be assessed using evidence of impact on subjects' functioning and overall well-being as well as subjects' utilization of health

resources and loss of time from work. Thus, PRO endpoints will also be utilized in the study.

The safety assessments used in this study are standard, widely used and generally recognized as reliable, accurate and relevant within the context of this study design.

For measurement of endometrial health, TVU has been selected as a reliable and established clinical assessment tool. TVU will also be utilized for evaluation of subjects for evidence of exclusionary gynecologic findings. Endometrial biopsy will provide a direct measure of any effect of elagolix on the endometrium.

DXA is a standard accepted measure of bone mineral density, and will be utilized to assess the effect of elagolix plus E2/NETA. Given the known relationship between estradiol levels and bone loss, serum E2 measurements will also be utilized to assess potential bone effects of elagolix plus E2/NETA.

5.6.3 Suitability of Subject Population

Premenopausal women 18 to 49 years of age with moderate to severe endometriosis-associated pain were selected for this study because this is the demographic that suffers from endometriosis with associated pain, including dyspareunia. No studies in males or females outside of their reproductive years are necessary for this indication.

5.6.4 Selection of Doses in the Study

Elagolix has a dose-dependent effect on BMD loss that is mediated through suppression of estradiol levels. Preliminary efficacy data from the completed Phase 3 clinical development program supports the ability of elagolix to reduce endometriosis-associated pain at both the 150 mg QD and 200 mg BID dose levels in a dose-dependent fashion (higher responder rate for 200 mg BID than for 150 mg QD). Also consistent with E2 suppression and findings from previous elagolix studies, there was a dose dependent effect on BMD, such that longer duration of treatment with the higher elagolix dose (200 mg BID) would likely require concomitant use of hormonal add back therapy to

mitigate BMD decrease. Furthermore, data from the Phase 2b study of elagolix in subjects with heavy menstrual bleeding due to uterine fibroids demonstrated the effect of E2/NETA on mitigating the BMD decrease associated with elagolix 300 mg BID. E2/NETA is approved for the prevention of osteoporosis in postmenopausal (estrogen-deficient) women.

As such, the elagolix 200 mg BID dose, in combination with E2/NETA add-back therapy was selected for this Phase 3 study, which will evaluate the safety and efficacy of this regimen in premenopausal women with moderate to severe endometriosis-associated pain. The objective is to generate data that would support a longer duration of use of this regimen for the proposed indication of management of endometriosis with associated pain, similar to the ongoing Phase 3 registration program.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.5. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an 'Other' cause of the event. For adverse events to be

considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All adverse events should be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Any worsening of a subject's endometriosis-associated pain during the course of the study will not be captured as an adverse event unless it meets the criteria for a serious adverse event (Section 6.1.1.2), at which point, it will be reported as such. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities, changes in BMD (during the Treatment Period) and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the Investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed

earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events of Special Interest

Some adverse events, such as SAEs and adverse events of special interest (AESI), may require additional information to be collected, including family history. AESIs include, but are not limited to rash/hypersensitivity, fracture, neuro-psychiatric (depression, mood swings, etc.) and vasomotor symptoms (e.g., hot flush, night sweats).

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

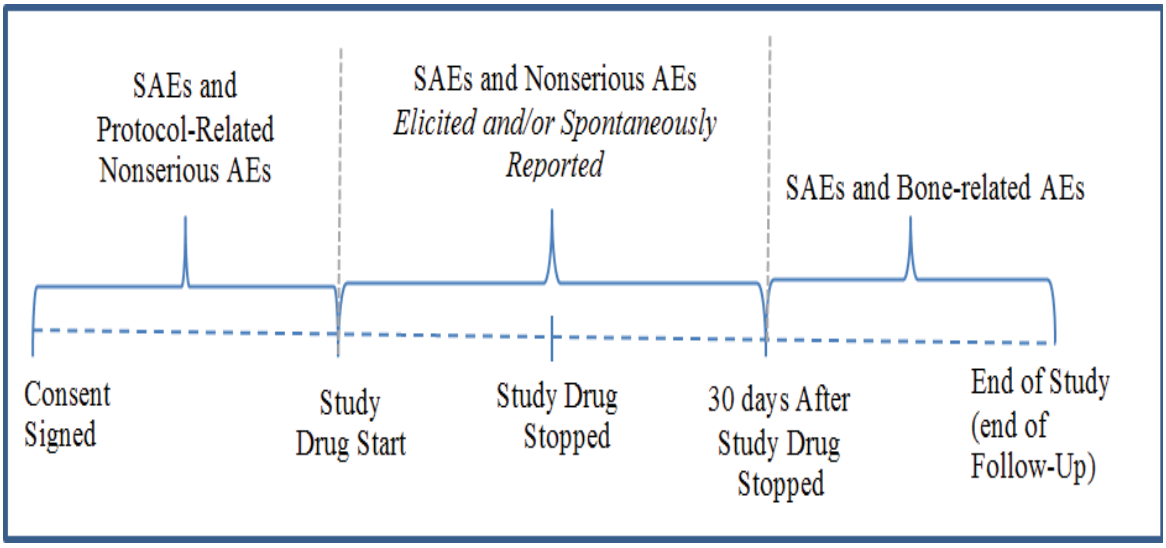
If an Investigator's opinion of "no reasonable possibility of being related to study drug" is given, another cause of event must be provided by the Investigator for serious adverse events.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug have elapsed will be collected, whether solicited or spontaneously reported by the subject. All nonserious adverse events of bone fracture, clinically significant BMD loss, or newly diagnosed medically-related bone condition will be collected during the Follow-Up Period, until the subject discontinues from study participation. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Men's and Women's Health Safety Team at:

Men's and Women's Health Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Men's and Women's Health Safety Line
Phone: [redacted]
Fax:
Email:

For any subject safety concerns, please contact the AbbVie Therapeutic Area Scientific Director listed below who will discuss with the AbbVie TA Medical Director as needed.

[redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Scientific Director is not available by telephone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the Treatment or Follow-Up Periods of the study must be discontinued (Section 5.4 and Section 5.4.1). A positive urine pregnancy test result must be confirmed with a serum pregnancy test. While waiting for the results of the serum pregnancy test, study drug should be temporarily discontinued pending results of the serum pregnancy test. If a serum pregnancy test result is positive at any time during the Treatment Period of the study, the site will immediately inform the subject to discontinue study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for any study subject with a positive serum pregnancy test from the signing of the informed consent (i.e., washout [if applicable] or screening) through completion of the Follow-Up Month 1 visit. The site will report a positive pregnancy test to the Sponsor, will follow the course of the subject's pregnancy, and report to the Sponsor on the health of the subject and fetus at each trimester, the newborn at the first post-delivery pediatrician visit and the infant 6 – 12 months post-delivery.

If the subject becomes pregnant during the study, no additional study procedures, including protocol required DXA scans, will be conducted. However, an ultrasound examination will be performed as early as possible during the first trimester of pregnancy to assess the gestational age and document an intrauterine pregnancy. The following information on the outcome of a pregnancy that occurs after signing of the informed consent, regardless of when the subject became pregnant (i.e., either during the Washout, Screening, Treatment or through Follow-Up Month 1) should be collected: fetal outcome (e.g., spontaneous or elective abortion, live infant or still birth), date and mode of delivery, birth weight, birth length, gender, congenital anomaly and medically significant complications during pregnancy or labor or delivery. For live infant births, information on the health of the infant will be collected from the first post-delivery pediatrician visit and at 6 to 12 months after delivery.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome for mother or infant meeting any serious criteria including an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality by the product to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (investigational product). In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot

be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The Principal Investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned Clinical Monitor or the following AbbVie Clinical Study Team Members:

Primary Contact: Alternate Contact:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analysis Plans

8.1.1 General Considerations

The SAS system will be used to perform the statistical analyses. All statistical tests will be two-sided and a significance level of 0.05 will be used unless otherwise specified. A test will be deemed statistically significant if the *P* value rounded to three decimal places is less than or equal to 0.05 unless otherwise specified. The primary efficacy comparisons will be at Treatment Month 6 between the elagolix 200 mg BID plus E2/NETA treatment group (Group C) and elagolix 150 mg QD group (treatment Group B) in patients who are incomplete responders to elagolix 150 mg QD treatment at Month 3.

8.1.2 Data Sets Analyzed

The full analysis set is comprised of all enrolled subjects who took at least one dose of the study drug and subjects will be analyzed in the treatment regimen to which she was assigned. For the Open-label Run-in period (through Treatment Month 3) of the study, all subjects who receive at least 1 dose of study drug during the Open-label Run-in period will be included in the Open-label full analyses. For the Double-blind Period of the study (Months 4 – 24), all subjects who receive at least 1 dose of study drug during the Double-blind Period will be included in the Double-blind full analyses. The full analysis set will be used for all analyses unless otherwise specified in the SAP.

8.1.3 Demographic, Baseline Characteristics and Concomitant Medications

Demographic and baseline characteristics will be summarized by treatment groups as well as the following two groups:

- Subjects discontinued prior to the Double-blind Period.
- Subjects treated in the Double-blind Period.

Medical history, protocol deviations, premature discontinuations, concomitant medications, and study drug exposure will be summarized. No treatment group comparisons will be made. Unless noted otherwise, the baseline values will be defined as the last value obtained prior to the first dose of the study drug during the Open-label Run-in Period.

8.1.4 Efficacy

8.1.4.1 General Considerations

Analysis details for Months 1 through 24 of the Treatment Period will be specified in the SAP.

The primary efficacy comparisons will be at Treatment Month 6 between the Elagolix 200 mg BID plus E2/NETA treatment group (Group C) and elagolix 150 mg QD group (treatment Group B) in patients who are incomplete responders to elagolix 150 mg QD treatment at Month 3.

For efficacy data collected during Month 7 – 24 of the treatment period, summaries will be provided for the following treatment groups.

- Efficacy responders to elagolix 150 mg QD at Month 3 and continue treatment through Month 24 (Group A).
- Incomplete efficacy responders to elagolix 150 mg QD at Month 3 and randomized to elagolix 200 mg BID plus E2/NETA 1 mg/0.5 mg QD treatment group and continue treatment through Month 24 (Group C).
- Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 150 mg QD treatment group and remain incomplete efficacy responders at Month 6, dose increased to elagolix 200 mg BID plus E2/NETA 1 mg/0.5 mg QD through Month 24 (Group D).
- Incomplete efficacy responders to elagolix 150 mg QD at Month 3, randomized to elagolix 150 mg QD treatment group and are efficacy responders at Month 6 continue treatment through Month 24 (Group E).

8.1.4.2 Primary Efficacy Variable

8.1.4.2.1 Primary Analysis

The primary analysis of the co-primary endpoints will be performed using the Double-blind full analysis set.

The co-primary efficacy endpoints will be the proportion of responders at Month 6 based upon the mutually-exclusive scales for daily assessment of DYS and NMPP measured by the 4 point Endometriosis Daily Pain Impact Diary using the daily e-Diary.

For each of the co-primary endpoints, the criterion for defining a subject as a responder at Month 6 of the Treatment Period will include a reduction of X or greater from baseline in the average pain score as well as no increased analgesic rescue use for endometriosis-associated pain.

The subjects will record use of these rescue analgesic medications on a daily basis in the e-Diary for the first 6 months of the treatment period.

The definition of increased analgesic use is as follows:

- For the primary endpoints of DYS and NMPP, subjects will be considered non-responders if they have a 15% or greater increase from baseline in average pill count of rescue analgesics (endometriosis-associated) as further specified in Appendix H.

For the first 6 months, the rescue analgesic use for any defined period will be based on the average pill count during the analysis window for each class of rescue analgesics: NSAIDs, opioids, and any (NSAIDs and/or opioids). The total pill count for each class of rescue analgesic is the sum of the pill count of the corresponding class of rescue analgesic, as reported in the e-Diary during the time period of interest. For the purposes of the rescue analgesic analysis, the number of pills within each class of rescue analgesic (NSAID or opioid) will be considered equivalent, regardless of specific pill choice,

e.g., average NSAID pill count will consider all types of NSAIDs specified in Table 3 and will not be conducted separately by NSAID type.

For both DYS and NMPP, responses of "None," "Mild," "Moderate," and "Severe" will be assigned a score of 0, 1, 2, and 3, respectively.

The average pain score for DYS or NMPP for Month 6 will be based on a 35 day window. If a subject's mean score for dysmenorrhea is undefined numerically for a time point because her daily e-Diary reports indicate she did not experience her period on any days during the 35 calendar day time period, then mean score for DYS for that time point will be set equal to zero (which reflects the absence of any dysmenorrhea during that reporting time period).

For each of the co-primary endpoints, the criterion for defining a subject as a pain responder at Month 6 will be a reduction of X or greater from baseline. The threshold for response in the responder analysis (i.e., the value of X) will be chosen to represent a clinically meaningful reduction in pain. The threshold will be determined based on a ROC analysis using the PGIC at Month 6 as an anchor and change from baseline at Month 6. The PGIC is a 7-point response scale: "Since I started taking the study medication, my endometriosis related pain has: very much improved (1), much improved (2), minimally improved (3), not changed (4), minimally worse (5), much worse (6), very much worse (7)."

The responses of "much improved" and "very much improved" on PGIC will be used to define responders, and the threshold for response (the value of X) will be chosen to balance sensitivity and specificity. That is, it will be the value that corresponds to the point on the ROC curve that is closest to the upper left corner when plotting 1-specificity versus sensitivity, i.e., closest to 100% sensitivity and 100% specificity. No other covariates will be included in the ROC analysis.

The ROC analysis may identify different response thresholds for DYS and NMPP. The results of the ROC analysis, containing the determined thresholds, will be included in the final SAP prior to blind break.

The primary analysis of the co-primary endpoints will be based on a logistic regression model including treatment as the main factor and baseline pain score as a covariate to compare the proportion of responders at Month 6 between the incomplete responder groups that were randomized at Month 3 to either the elagolix 200 mg BID plus E2/NETA treatment group (Group C) or elagolix 150 mg QD group (Group B).

The primary analysis will be repeated where the responder/non-responder categorization will use percent change from baseline in pain reduction. ROC thresholds based on percent change from baseline in the average pain score will be conducted in the same manner as for the change from baseline.

Full details regarding the ROC analysis will be provided in the SAP.

8.1.4.3 Secondary Efficacy Variables

Key Secondary Efficacy Endpoints

The following key secondary efficacy endpoints based on data collected during the first 6 months of the treatment period will be summarized by treatment regimen:

- Change from baseline in DYS
- Change from baseline in NMPP
- Change from baseline in dyspareunia
- Change from baseline in Daily Diary endometriosis-associated pain score via NRS
- Change from baseline in rescue analgesic use across both classes of rescue analgesics based on average pill counts
- Percentage of subjects with 30% or more reduction from baseline based on the 35 day mean of the Daily Diary endometriosis-associated pain score via NRS

Additional details regarding the key secondary efficacy endpoints will be provided in the SAP.

Additional Secondary Efficacy Endpoints

Additional secondary efficacy endpoints based on data collected during the first 6 months of the treatment period will include the following.

- Proportion of responders as assessed by change and percent change from Baseline in average pain score and rescue analgesic use monthly for DYS, NMPP, dyspareunia, and Daily Diary endometriosis-associated pain score via NRS, respectively.
- Proportion of responders as assessed by change and percent change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP, dyspareunia, and Daily Diary endometriosis-associated pain score via NRS respectively.
- Change and percent change from Baseline, in the monthly average pain score (DYS, NMPP, dyspareunia), and Daily Diary endometriosis-associated pain score via NRS.
- Change from Baseline in rescue analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary.
- Proportion of analgesic use responders monthly (based only on reduction of rescue analgesics used).

Additional secondary efficacy endpoints during the 24 months treatment period will include the following.

- Patient Global Impression of Change (PGIC).
- Monthly site administered overall endometriosis-associated pain questionnaire (7-day recall).
- Patient reported outcome (PRO) and outcomes Rating Scales questionnaires.

Summaries for Secondary Efficacy Variables

Unless otherwise specified, no statistical tests will be performed for secondary efficacy endpoints.

Analysis details will be specified in the SAP.

8.1.4.3.1 Dysmenorrhea and Non-Menstrual Pelvic Pain

The proportion of responders, mean change and percent change from baseline to each visit during the first 6 months treatment period in DYS and NMPP will be summarized for each monthly visit.

8.1.4.3.2 Dyspareunia

The proportion of responders, mean change and percent change from baseline to each visit during the first 6 months of the Treatment Period in dyspareunia will be summarized similar to the method for DYS and NMPP.

8.1.4.3.3 Rescue Analgesic Use for Endometriosis-Associated Pain

The use of rescue analgesics for endometriosis-associated pain will be reported by study subjects in the e-Diary during the first 6 months of the Treatment Period.

The rescue analgesic for endometriosis-associated pain taken by the subject will be summarized for the following analgesic categories: (a) NSAID or opioid, (b) opioid and (c) NSAID.

Baseline will be calculated as percentage of days of endometriosis rescue analgesic use for each analgesic category during the last 35 calendar days prior to and including Day 1 during the Screening Period. For the purposes of the rescue analgesic analysis, the number of pills within each class of rescue analgesic (NSAID or opioid) will be considered equivalent, regardless of specific pill choice, e.g., average NSAID pill count will consider all protocol specified NSAIDs specified in Table 3 and will not be conducted separately by NSAID type.

The average pill count for each class of rescue analgesic for each visit during the first 6 months of the treatment period will be calculated by adding the daily pill count of the corresponding class of rescue analgesic in the analysis and dividing over the length of the window, generally equal to 35. For Month 1, average values will be based on data collected between Study Day 1 and the Month 1 reference study day. For Month 4, average values will be based on data collected between Month 3 reference study day and Month 4 reference study day.

8.1.4.3.4 Daily Diary Endometriosis-Associated Pain Score via NRS

The proportion of responders, mean change and percent change from baseline to each visit during the first 6 months treatment period in Daily Diary endometriosis-associated pain score via NRS will be summarized for each monthly visit.

8.1.4.3.5 Additional Endpoints

The additional variables including PGIC, overall endometriosis-associated pain via NRS (11-point NRS, 7-day recall), EHP-30, EQ-5D-5L, WPAI, HCRU, ETSQ and PROMIS Fatigue short Form 6a will be summarized during the 24 months treatment period.

8.1.5 Safety

8.1.5.1 General Considerations

All enrolled subjects who took at least one dose of the study drug will be included in the safety analyses.

Data collected during the 3 month Open-Label Run-In Period will be summarized for all subjects combined.

For safety data collected during Treatment Months 4 – 6, summaries will be presented for the following groups.

- Subjects who are responders to Elagolix 150 mg QD treatment group at Month 3 (Group A) and subjects who are incomplete responders to Elagolix

150 mg QD treatment group at Month 3 and randomized to Elagolix 150 mg QD treatment group at Month 3 (Group B) will be combined

- Subjects who are incomplete responders to Elagolix 150 mg QD treatment group at Month 3 and randomized to Elagolix 200 mg BID plus E2/NETA treatment group at Month 3 (Group C).

For safety data collected during Treatment Months 7 – 24, summaries will be presented for the following group.

- Subjects who are responders to Elagolix 150 mg QD treatment group at Month 3 (Group A) and subjects who are incomplete responders to Elagolix 150 mg QD treatment group at Month 3 and randomized to Elagolix 150 mg QD treatment group at Month 3 and are responders at Month 6 and continue to receive Elagolix 150 mg QD (Group E) will be combined.
- Subjects who are incomplete responders to Elagolix 150 mg QD treatment group at Month 3 and randomized to Elagolix 150 mg QD treatment group at Month 3 and are incomplete responders at Month 6 and are switched to Elagolix 200 mg BID plus E2/NETA (Group D).
- Subjects who are incomplete responders to Elagolix 150 mg QD treatment group at Month 3 and randomized Elagolix 200 mg BID plus E2/NETA treatment group at Month 3 (Group C).

Baseline for all subjects will refer to the data obtained prior to dosing on Day 1 of the Open-label Run-in Period.

In general, for continuous variables, descriptive statistics (mean, standard deviation, median, minimum and maximum) will be summarized by treatment group. Categorical data will be summarized with frequencies and percentages by treatment group. Unless otherwise specified, no statistical tests will be performed.

Analysis details will be specified in the SAP.

8.1.5.2 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment-emergent adverse events (TEAEs) will be summarized. TEAEs are defined as AEs with a start date on or after the first dose of the study drug and within 30 days of the last dose of the study drug. AEs starting more than 30 days following discontinuation of the study drug will not be included in the summaries of TEAEs.

Frequencies and percentages of subjects with TEAEs will be calculated for each treatment group as follows:

- Any event
- By system organ class, and preferred term
- By system organ class, preferred term and maximum relationship
- By system organ class, preferred term and maximum severity
- Any event and by system organ class and preferred term for events resulting in study drug discontinuation
- Any event and by system organ class and preferred term for serious events
- Any event and preferred term for AESIs (e.g., hypoestrogenic adverse events)

8.1.5.3 Analysis of Laboratory Data and Vital Signs

Changes in laboratory and vital sign parameters will be summarized as specified in the SAP.

8.1.5.4 Bone Mineral Density

The key BMD evaluations are lumbar spine at Month 12 and Month 24. Secondary BMD endpoints include total hip and femoral neck.

The Z- and T-scores and BMD percent change from baseline values during the 24 month treatment period will be summarized. Factors associated with a change in BMD will be

explored. Unless otherwise specified, no statistical comparisons on BMD assessment will be performed between treatment groups.

Full analysis details will be provided in the SAP.

Post-treatment bone mineral density scans will be summarized similarly, as appropriate.

8.1.5.5 Uterine Bleeding

Descriptive statistics for uterine bleeding as collected in the daily e-Diary will be presented.

8.1.5.6 Endometrial Variables

Endometrial biopsy result and ultrasound assessments will be summarized.

8.2 Pharmacokinetics/Pharmacodynamics

Plasma concentrations of elagolix and norethindrone and serum concentrations of estradiol will be listed for each subject by visit day and dose regimen, as applicable. Pharmacokinetic data may be combined with data from other studies in women. Exposure-response analyses may be conducted as appropriate. For example, if pharmacokinetic exposures are estimated, analyses may be conducted to assess the relationship of pharmacokinetic parameters and estradiol concentrations, versus efficacy and safety. Additional analyses will be performed if useful and appropriate.

8.3 Determination of Sample Size

This study plans to enroll approximately 890 subjects to ensure a sufficient number of subjects receive elagolix 150 mg QD for 24 months.

Assuming the efficacy responder rate for the Daily Diary endometriosis-associated pain score via NRS is 50% during the open label elagolix 150 mg QD group at Month 3, 50% of subjects who complete Month 3 of the open-label period and are incomplete responders to 150 mg QD will be randomized in equal ratio to 150 QD and 200 BID plus E2/NETA.

Among those, assuming Month 6 DYS and NMPP responder rates of 20% for subjects who are randomized to elagolix 150 mg QD group (Group B) and 50% for subjects who are randomized elagolix 200 mg BID plus E2/NETA treatment group (Group C), this sample size provides greater than 90% power to detect a difference in response rate based on a 2-sided test at the significance level of $\alpha = 0.05$. The above sample size was calculated using nQuery advisor 7.0.

Assuming 80% of incomplete responders to 150 mg QD who are randomized to 150 QD at Month 3 are switched to elagolix 200 mg BID plus E2/NETA at Month 6 and a 25% completion rate, the current sample size will provide at least 120 subjects who receive elagolix 150 mg QD treatment group for 24 months (Group A and E).

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory

Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker

samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional exploratory research. The nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the optional exploratory research, it will not impact their participation in the study.

In the event a subject withdraws from the main study, optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded to the appropriate source document. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from

investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's eCRF data. It will be possible for the Investigator to make paper printouts from that media.

Electronic Patient Reported Outcomes (ePRO)

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) tool called TrialMax®, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO tool is available through the vendor, CRF Health, while the user acceptance testing of the study-specific PRO design will be conducted and maintained at AbbVie.

The subject will enter the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the trial. This access will be available for the duration of the trial to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO tool will be archived on appropriate data media (CD-ROM, etc.) and provided to the Investigator at that time as a durable record of the site's ePRO data. It will be possible for the Investigator to make paper print-outs from that media.

The ePRO diary data will be collected electronically via a handheld device into which the subject will record the required pieces of information on a daily basis. The electronic device will be programmed to allow data entry for diary data being collected outside the clinic. Data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by CRF Health. The Investigator

and delegated site staff will be able to access all uploaded subject entered data via a password protected website up until the generation, receipt and confirmation of the study archive.

The EHP-30, EQ-5D-5L, WPAI:SHP, PROMIS Fatigue Short Form 6a, ETSQ and the PGIC questionnaires and some information regarding some modifiable and non-modifiable risk factors possibly related to BMD (e.g., IPAQ, dietary calcium intake questions) will be collected electronically via a tablet device into which the subject will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessments at any one visit. The subject's response to the monthly site administered Overall Endometriosis-Associated Pain via NRS (7-day recall) will be entered electronically via a tablet device by site staff. All data entered on the device will be immediately stored to the device itself and automatically uploaded to a central server administrated by CRF Health. The Investigator and delegated site staff will be able to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, a Site Training Visit will be held with AbbVie personnel (and/or their representatives), the investigators, and the appropriate site personnel. This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, eCRF completion, and specimen collection methods. The personnel at the study site will be trained on the study procedures, when applicable, by an AbbVie monitor or designee.

The AbbVie monitor or designee will monitor the study site throughout the study. A source document review will be performed against entries on the eCRFs and a quality assurance check will be performed to ensure that the Investigator is complying with the

protocol and regulations. Remote review of data will also be performed. In addition, ongoing review of the data will be conducted by a physician or representative at AbbVie.

Data entered into eCRFs will be electronically transferred to AbbVie and imported into the database using validated software throughout the study. Computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Routine hematology, serum chemistry, vitamin D, serum lipid and endocrine panels, serum pregnancy tests, urinalysis, Pap tests (colposcopy plus biopsy, if applicable) and endometrial biopsies will be analyzed using a central laboratory. The data from these analyses will be electronically transferred from the central laboratory to the study database.

A review of all laboratory results will be conducted by a physician and clinical review team at AbbVie, the AbbVie monitors (or their representatives), the Investigator and other appropriate personnel from AbbVie.

Pharmacokinetic and pharmacodynamic samples will be analyzed by the Drug Analysis Department at AbbVie and data will be loaded into the study database.

Transvaginal ultrasounds will be read by the central imaging vendor. The results of these scans will be electronically transferred from the central imaging vendor to the study database.

DXA scans will be read by a central imaging vendor. The results of these scans will be electronically transferred from the central imaging vendor to the study database.

12.0 Use of Information

All information concerning elagolix and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation

information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of elagolix. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, telephone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by AbbVie.

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to Investigators and used in scientific publications or presented at

medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The Investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the Investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the Investigator and AbbVie. The Investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The Investigator must retain any records related to the study according to ICH GCP and local requirements. If the Investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory Investigator from the investigators who participate in the study. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory Investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit/last procedure.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for elagolix (ABT-620).
2. I have read this protocol and agree that the study is ethical.
3. I have read the Package Insert/Product Label for E2/NETA.
4. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
5. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
6. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title: A Study to Evaluate Safety and Efficacy of Elagolix Alone or Elagolix with Hormonal Add-Back in Subjects with Endometriosis with Associated Moderate to Severe Pain

Protocol Date: 29 September 2017

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

1. Kennedy SH, Moore SJ. The investigation and management of endometriosis. Royal College of Obstetricians and Gynecologists Guideline Number 24, 2nd ed. October 2006. p. 1-14.
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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
		Clinical Operations
		Clinical Pharmacokinetics
		Bioanalysis
		Clinical Development
		Statistics

Appendix C. Study Activities

Study Activities – Washout, Screening and Treatment Periods

Activity	Washout[b]	Screening	Treatment Period[a]						
			Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Informed Consent	X	X[d]							
Medical History[e]	X	X[f]	X[f]						
Smoking/Alcohol Assessment		X							X
Physical Exam	X[g]	X[h]	X[g]						
Gynecological (External Genitalia, Pelvic and Breast) Exam		X							
12-lead ECG		X							
Vital Signs	X	X	X	X	X	X	X	X	X
Mammogram[i]		X							
TVU[j]		X							
DXA		X							X
Pap smear		X							
Pregnancy Tests[j,k,l] Urine (u) serum (s)	X (u)	X (u, s)	X (u, s)	X (u)	X (u)	X (u, s)	X (u)	X (u)	X (u, s)
Endometrial Biopsy[m]		X							
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis		X	X						X
Vitamin D Testing		X	X						X

Activity	Washout[b]	Screening	Treatment Period[a]						
			Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase						X			
Hepatitis/HIV Screen		X							
Reflexive Thyroid Stimulating Hormone		X							
Urine Test for Gonorrhea and Chlamydia (optional)[n]		X							
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X[o]			X[o]
Pharmacodynamic Sample (E2)			X[p]	X	X	X[o]	X	X	X[o]
E-Diary Daily Entry Endometriosis Daily Pain Impact Diary, Daily Diary endometriosis-associated pain score via NRS, Dyspareunia, Uterine Bleeding, Rescue Analgesic Use for Endometriosis-Associated Pain		X	X	X	X	X	X	X	X
Endometriosis Health Profile-30 (EHP-30)			X			X			X
EuroQol-5D 5 level (EQ-5D-5L)			X			X			X
Endometriosis Treatment Satisfaction Questionnaire (ETSQ)			X			X			X
PROMIS Fatigue Short Form 6a, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)			X						X

Activity	Washout[b]	Screening	Treatment Period[a]						
			Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
IPAQ and Dietary Calcium Intake Questionnaire			X						X
Health Care Resource Utilization (HCRU)			X	X	X	X	X	X	X
Overall endometriosis-associated pain via NRS (11-point NRS, 7-day recall)[q]			X	X	X	X	X	X	X
PGIC				X	X	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening		X	X						
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit						X			X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn) & Birth Control Attestation	X	X	X	X	X	X	X	X	X
Randomization[r]						X			
Dispense Study Drug			X	X	X	X[s]	X	X	X[s]

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Telephone Contact	X		X		X	
Physical Exam						X[h]
Gynecological (External Genitalia, Pelvic and Breast) Exam						X[h]
Vital Signs		X		X		X
TVU[j]						X
DXA						X
Pregnancy Test:[j,k,l] Urine (u) serum (s)	X (u)	X (u, s)	X (u)	X (u)	X (u)	X (u, s)
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis						X
Vitamin D Testing						X
Subset of Chemistry Labs: ALT, AST, Alkaline Phosphatase		X				
Pharmacokinetic Sample (elagolix and norethindrone concentration)				X		X
Pharmacodynamic Sample (E2)		X		X		X
Smoking/Alcohol Assessment						X
• Endometriosis Health Profile-30 (EHP-30) • EuroQol-5D 5 level (EQ-5D-5L) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) • ETSQ						X
IPAQ and Dietary Calcium Intake Questionnaire						X

Activity	Treatment Period[a]					
	Month 7	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**
Health Care Resource Utilization (HCRU)	X	X	X	X	X	X
Overall endometriosis-associated pain via NRS (11-point NRS, 7-day recall)[q]	X	X	X	X	X	X
PGIC		X		X		X
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit						X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling	X	X	X	X	X	X
Contraceptive Dispensing (prn)/Birth Control Attestation		X		X		X
Dispense Study Drug		X		X		X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18
Telephone Contact	X	X		X	X	
Vital Signs			X			X
DXA						X
Pregnancy Tests:[j,k,l] urine (u) serum (s)	X (u)	X (u)	X (u, s)	X (u)	X (u)	X (u, s)
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis						X
Vitamin D testing						X
Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X			
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X
Pharmacodynamic Sample (E2)			X			X
Smoking/Alcohol Assessment						X
• Endometriosis Health Profile-30 (EHP-30) • EuroQol-5D 5 level (EQ-5D-5L) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) • ETSQ						X
IPAQ and Dietary Calcium Intake Questionnaire						X
Health Care Resource Utilization (HCRU)	X	X	X	X	X	X

Activity	Treatment Period[a]					
	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18
Overall endometriosis-associated pain via NRS (11-point NRS, 7-day recall)[p]	X	X	X	X	X	X
PGIC			X			X
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit						X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling	X	X	X	X	X	X
Contraceptive Dispensing (prn)/Birth Control Attestation			X			X
Dispense Study Drug			X			X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]						
	Month 19	Month 20	Month 21	Month 22	Month 23	Month 24	PD[t]
Telehone Contact	X	X		X	X		
Physical Exam						X[h]	X[h]
Gynecological (External Genitalia, Pelvic and Breast) Exam						X[h]	X[g]
Vital Signs			X			X	X
TVU[j]						X	X[t]
DXA[l]						X	X[t]
Pap test						X	X[t]
Pregnancy Tests: [j,k,l] urine (u) serum (s)	X (u)	X (u)	X (u, s)	X (u)	X (u)	X (u, s)	X (u, s)
Endometrial Biopsy[m]						X	X[t]
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis						X	X
Vitamin D testing						X	X
Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X				
Urine Test for Gonorrhea and Chlamydia (Optional)[n]						X	X
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X	X
Pharmacodynamic Sample (E2)			X			X	X
Health Care Resource Utilization (HCRU)	X	X	X	X	X	X	X

Activity	Treatment Period[a]						
	Month 19	**Month 20**	**Month 21**	**Month 22**	**Month 23**	**Month 24**	**PD[t]**
Smoking/Alcohol Assessment						X	
• Endometriosis Health Profile-30 (EHP-30) • EuroQol-5D 5 level (EQ-5D-5L) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) • ETSQ						X	X
IPAQ and Dietary Calcium Intake Questionnaire						X	X (IPAQ only)
Overall endometriosis-associated pain via NRS (11-point NRS, 7-day recall)[p]	X	X	X	X	X	X	X
PGIC			X			X	X
Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit						X	
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X	X
Contraceptive Counseling	X	X	X	X	X	X	X[u]
Contraceptive Dispensing (prn)/Birth Control Attestation			X			X	
Dispense Study Drug			X				

a. The window for visits during the Treatment Period is ± 5 days of the scheduled date.

b. Subjects using exclusionary hormonal therapy for endometriosis or hormonal contraceptives must discontinue these therapies during the Washout Period. Informed consent must be obtained prior to entering a subject in washout or performing any study specific procedures.

c. Day 1 will occur between Days 1 to 10 of the onset (first day with full menstrual flow) of menses. All activities should be completed prior to dosing.
d. For subjects who completed the Washout Period, it is not required to repeat the informed consent.
e. Includes Gynecological/Endometriosis History.
f. Update prior to dosing as needed.
g. Brief, symptom-directed examination.
h. Complete physical examination, including weight. The subject should wear lightweight clothing and no shoes during weighing.
i. For subjects who are ≥ 39 years of age or older at the start of screening, if no mammogram has been performed within 3 months. If a subject has a mammogram performed during screening, annual mammograms should be performed during study participation. Mammograms will be read locally.
j. For any subject who has a positive serum pregnancy test result during the Treatment Period, a TVU must be conducted as early as possible in the first trimester in order to assess the conception date. The subject will be discontinued from the study at the point the serum pregnancy test is confirmed positive.
k. A positive urine pregnancy test result must be confirmed with a serum pregnancy test.
l. Urine pregnancy tests will be self-administered at home by the study subject at Treatment Months 7, 9, 11, 13 – 14, 16 – 17, 19 – 20 and 22 – 23. Subjects will self-administer the at home urine pregnancy tests (kits provided by the central laboratory) and report the results to the site at the telephone contact visits.
m. A negative urine pregnancy result should be obtained on the day of endometrial biopsy, prior to performing the procedure. For subjects with an insufficient endometrial biopsy at Month 24 whose concurrent TVU indicates an endometrial thickness > 4 mm, a repeat biopsy should be performed.
n. Urine test for gonorrhea chlamydia should be performed prior to undergoing the endometrial biopsy. Positive test results will be treated outside of the protocol.
o. To be collected prior to study drug dispensation/dosing at the site.
p. On Day 1, the Pharmacodynamic sample should be collected with the safety labs prior to dosing.
q. Overall endometriosis-associated pain will be assessed via an 11-point numeric rating scale (NRS [0 – 10]) that will be administered to the subject by site staff.
r. Based on assessment for incomplete efficacy responders and subsequent blinded treatment assignment.
s. Subjects will be administered the first dose of study drug from the new study drug kit(s) assigned at the investigative site (and prior to collection of PD sample).
t. Premature Discontinuation prior to Month 6 does not require a DXA, TVU, Pap test, or endometrial biopsy.
u. If the subject prematurely discontinues, the site should counsel the subject on the continued use of non-hormonal contraceptive use for at least 30 days after the last dose of study drug.

Study Activities – Follow-Up Period

Activity	Follow-Up Period[a]		
	Month 1	Month 6	Month 12
DXA		X[b]	X[b]
Physical Exam[c]	X		
Pharmacodynamic Sample (E2)	X	X	X
FSH sample	X		
Pregnancy Test	X[d] (u, s)	X[e] (u)	X[e] (u)
Review Adverse Events	X[f]	X[g]	X[g]
Concomitant Medication	X[e]	X	X
Follow up of Menstruation Questionnaire[h]	X[i]		

a. The Follow-Up Period for the study will conclude for all subjects 30 days after the last Treatment Visit.

b. DXA scans of the lumbar spine, total hip, and femoral neck will be obtained at Follow-Up Months 6 and/or 12 for those subjects whose follow-up period visits occur prior to the study conclusion.

c. Brief, symptom-directed examination to assess any ongoing AEs for resolution.

d. A positive urine pregnancy test result must be confirmed with a serum pregnancy test. For any subject who has a positive serum pregnancy test result during the Follow-Up Period, a TVU must be conducted as early as possible in the first trimester in order to assess the conception date. The subject will be discontinued from the Follow-Up Period at the point the pregnancy is confirmed.

e. A negative urine pregnancy test must be obtained on the date of (or within 2 days prior) the DXA, prior to performing the procedure. A positive urine pregnancy test result must be confirmed with a serum pregnancy test. For any subject who has a positive serum pregnancy test result, the DXA should not be performed. The subject will be discontinued from the Follow-Up Period at the point the pregnancy is confirmed.

f. Any ongoing AEs and concomitant medications at the end of the Treatment Period will be reviewed for resolution during this visit.

g. Only AESIs of bone fracture, clinically significant BMD loss, or newly diagnosed medically-related bone condition will be collected during the Follow-Up Period.

h. If the subject has a documented menstrual period after the last dose of study drug returned, the subject may begin the use of hormonal contraception (e.g., oral or IUD) in place of non-hormonal birth control.

i. If subject has not returned to menses by Follow-Up Month 1, continue to follow.

Appendix D. BI-RADS Classification

The BI-RADS assessment categories are:

- 0 – Incomplete
- 1 – Negative
- 2 – Benign
- 3 – Probably benign
- 4 – Suspicious
- 5 – Highly suggestive of malignancy
- 6 – Known biopsy-proven malignancy

Sickles EA, D'Orsi CJ, Bassett LW, et al. ACR BI-RADS® Mammography. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013.

Appendix E. Overall Endometriosis-Associated Pain Questionnaire

On a scale of 0 – 10, 0 being no pain and 10 being worst pain ever, tell me the one number that describes your endometriosis pain at its WORST over the last 7 days.

Appendix F. Patient Global Impression of Change (PGIC)

Since I started taking the study medication, my endometriosis related pain has:

- ☐ Very much improved
- ☐ Much improved
- ☐ Minimally improved
- ☐ Not changed
- ☐ Minimally worse
- ☐ Much worse
- ☐ Very much worse

Appendix G. BMD Risk Factor Assessment Questionnaire

This questionnaire will help estimate the amount of calcium you get from you what you eat and drink.

Below is a list of some food items. For each item in the list, please enter the number of servings you have eaten or drank, on a typical or average day, during the past week.

Please note that if you eat more than the listed serving size or amount, then you would increase the number of servings accordingly. For example, if you have 1 cup of milk with breakfast and 1 cup of milk with dinner, you would enter 2 for the number of servings. Or if you have 3 slices of cheese pizza, you would enter 3 for the number of servings.

Food Type	Standard Serving Size	Number of Servings on Average
Dairy		
Skim Milk (non-fat)	8 ounces	
Soy milk (calcium-fortified)	8 ounces	
2% Milk	8 ounces	
Whole Milk	8 ounces	
Milk (buttermilk, lowfat)	8 ounces	
Yogurt (plain, low fat)	8 ounces	
Yogurt (fruit, low fat)	8 ounces	
Frozen yogurt (vanilla, soft serve)	½ cup	
Ice cream (vanilla)	½ cup	
Mozzarella cheese (part skim)	1½ ounces	
Cheddar cheese	1½ ounces	
Sour cream (reduced fat)	2 tablespoons	
Cottage cheese (1% milk fat)	1 cup	
Cream cheese (regular)	1 tablespoon	

Food Type	Standard Serving Size	Number of Servings on Average
Vegetables, Fruits, Nuts and Beans		
Turnip greens (fresh, boiled)	½ cup	
Broccoli (raw)	½ cup	
Kale (fresh, cooked)	1 cup	
Kale (raw, chopped)	1 cup	
Chinese cabbage (bok choy raw, shredded)	1 cup	
Orange juice (with calcium)	6 ounces	
Fish and Tofu		
Sardines (canned in oil, with bones)	3 ounces	
Canned pink salmon (with bones)	3 ounces	
Tofu (soft, made with calcium sulfate)	½ cup	
Tofu (firm, made with calcium sulfate)	½ cup	
Other		
Ready to eat cereal (calcium-fortified)	1 cup	
Bread (white)	1 slice	
Bread (whole-wheat)	1 slice	
Tortilla (corn, ready to bake/fry)	one 6" diameter	
Tortilla (flour, ready to bake/fry)	one 6" diameter	
Chocolate Pudding (refrigerated ready to eat)	4 ounces	

Appendix H. Analgesic Change During Treatment Period

Use of No Analgesics at Baseline		
Analgesic used during Screening	**Analgesic dose status at end of study**	**Responder?***
None	None	Responder
	Opioid analgesic and/or NSAID is started	Nonresponder
Use of Only NSAID at Baseline		
Analgesic used at Baseline	**Analgesic dose status at end of study**	**Responder?***
NSAID	Dose stopped, decreases, or is stable**	Responder
	Dose increases by 15% or more	Nonresponder
	Opioid analgesic is substituted or added	Nonresponder
Use of Only Opioid Analgesic at Baseline		
Analgesic used at Baseline	**Analgesic dose status at end of study**	**Responder?***
Opioid analgesic	Dose stopped, decreases, or is stable**	Responder
	Dose stopped and NSAID substituted (any dose)	Responder
	Dose decreases and NSAID added (any dose)	Responder
	Dose stable** and NSAID added (any dose)	Nonresponder
	Dose increases by 15% or more	Nonresponder
Use of NSAID and Opioid Analgesic at Baseline		
Analgesics used at Baseline	**Analgesic dose status at end of study**	**Responder?***
NSAID + opioid analgesic	NSAID dose stops + opioid analgesic use stops, decreases, or is stable**	Responder
	NSAID use stops + opioid analgesic dose increases by more than 15%	Nonresponder
	NSAID dose decreases + opioid analgesic use stops, decreases, or is stable**	Responder
	NSAID dose decreases + opioid analgesic dose increases by more than 15%	Nonresponder
	NSAID dose stable** + opioid analgesic use stops, decreases, or is stable**	Responder
	NSAID dose stable** + opioid analgesic dose increases by more than 15%	Nonresponder
	NSAID dose increases by more than 15% + opioid analgesic use stops	Responder

Use of NSAID and Opioid Analgesic at Baseline		
Analgesics used at Baseline	**Analgesic dose status at end of study**	**Responder?***
NSAID + opioid analgesic (continued)	NSAID dose increases by more than 15% + opioid analgesic dose decreases	Responder
	NSAID dose increases by more than 15% + opioid analgesic dose is stable**	Nonresponder
	NSAID dose increases by more than 15% + opioid analgesic dose increases by 15% or more	Nonresponder

* Analgesic Responder = Defined as a subject who meets the criteria for no increase in analgesic use.

** Stable = Dose is the same as the baseline dose or increases by less than 15% of the baseline dose.

Assessment of dose is based on number of tablets of NSAIDS/opioids recorded in the Daily e-diary.

Document Approval

Study M16383 - A Study to Evaluate Safety and Efficacy of Elagolix Alone or Elagolix with Hormonal Add-Back in Subjects with Endometriosis with Associated Moderate to Severe Pain - 29Sep2017

Version: 1.0 **Date:** 01-Oct-2017 05:33:11 PM **Company ID:** 10012017-00F9F683A6A0B8-00001-en

Signed by:	Date:	Meaning Of Signature:
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