1.0 Title Page

Clinical Study Protocol M14-702

A Phase 3 Study to Evaluate the Safety and Efficacy of Elagolix in Combination with Estradiol/Norethindrone Acetate in Subjects with Moderate to Severe Endometriosis-Associated Pain

Incorporating Administrative Change 1 and Amendments 1, 2, 3, and 4

AbbVie Investigational Product:	Elagolix (ABT-620)
Date:	27 March 2020
Development Phase:	3
Study Design:	This study employs a randomized, double-blind, placebo-controlled design during the first 12 months of the Treatment Period. The remaining 36 months of the Treatment Period is open-label, active treatment
Investigators:	Multicenter Trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted], MD, PhD [redacted] General Medicine, AbbVie 1 North Waukegan Road North Chicago, IL 60064 Phone: [redacted] Cell:

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.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	04 February 2016
Amendment 1	02 June 2017
Amendment 2	04 September 2018
Administrative Change 1	09 May 2019
Amendment 3	02 July 2019

The purpose of this amendment is to:

- Update Section 1.2, Synopsis.

  Rationale: *To ensure the Synopsis is consistent with the protocol amendment revisions.*
- Update Section 1.2, Introduction

  Rationale: *To incorporate language form the most current Investigator's Brochure.*
- Update Section 5.1, Overall Study Design and Plan: Description, Screening Period, and Section 8.1.6.3.3, Analgesic Use for Endometriosis-Associated Pain

  Rationale: *To remove reference to equivalency of protocol-allowed rescue analgesics based on FDA/regulatory comments*
- Update Section 5.2.3.3, Prohibited Therapy, Table 2

  Rationale: *To prohibit GnRH antagonists other than study drug during the entire study duration*
- Update Section 5.3.1.1, Study Procedures, and Appendix C, Study Activities Table as follows:
  - Add ± 15 day window for mammograms performed during the Treatment Period
  - Modify the endometrial biopsy criteria during the Treatment Period

- Add guidance regarding completion of mammograms, DXAs, TVUs, endometrial biopsies, and Pap tests at premature discontinuation.
- Remove the Month 27 PD sample
- Add Month 42 Patient Reported Outcomes & Outcomes Rating Scales
- Clarify the Overall Endometriosis-Associated Pain questionnaire (11-point NRS) should be completed at the time of the visit.
- Modify language regarding completion of the Health Care Resource Utilization to align with the time points correctly noted in the Study Activities Table

Rationale: *Study procedures were reviewed and evaluated for relevance for safety monitoring, alignment with standard of care guidelines, and study endpoints*

- Update to Section 5.3.3, Efficacy Variables to add Secondary Variables and modify Additional Efficacy Variables

  Rationale: *To reflect changes made in the Statistical Analysis Plan (SAP) based on FDA/regulatory feedback*

- Update Section 6.1.6, Pregnancy, to change the reporting timeframe of pregnancies to within 24 hours of awareness, for sites

  Rationale: *To align with AbbVie reporting standards*

- Update Section 8.1.4, End of Placebo Controlled Treatment Period Analysis, to include available data (open-label and placebo-controlled) collected until the last subject completes Treatment Period Month 12

  Rationale: *To allow for inclusion of available safety and efficacy data in the interim lock*

- Update 8.1.5, Month 24 and Month 36 Analyses

  Rationale: *To update the subsection and header to reflect changes made to the SAP allowing for additional data analyses during the Treatment Period*

- Update Section 8.1.6, Efficacy

  Rationale: *To reflect updates made to the SAP*

- Section 15.0, Reference List,

  Rationale: *To ensure the most up-to-date information is provided*

- Correct administrative and typographical errors throughout the document.

An itemized list of all changes made to this protocol under this amendment can be found in Appendix J.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-702
Name of Study Drug: Elagolix (ABT-620)	**Phase of Development:** 3
Name of Active Ingredient: Elagolix sodium	**Date of Protocol Synopsis:** 27 March 2020
Protocol Title: A Phase 3 Study to Evaluate the Safety and Efficacy of Elagolix in Combination with Estradiol/Norethindrone Acetate in Subjects with Moderate to Severe Endometriosis-Associated Pain	
Objectives: The objectives of the study are to 1) assess the safety and efficacy of elagolix 200 mg administered twice daily (BID) in combination with estradiol 1 mg/0.5 mg norethindrone acetate (E2/NETA 1 mg/0.5 mg) once a day (QD) compared to placebo at 6 and 12 months; 2) to assess the effect of elagolix 200 mg BID in combination with E2/NETA (1 mg/0.5 mg) QD, on bone mineral density (BMD) compared to elagolix 200 BID alone at 6 months, and compared to placebo at 6 months and at 12 months of treatment and 3) to evaluate the continued safety and efficacy of elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD for up to 48 months in the management of premenopausal women with moderate to severe endometriosis-associated pain.	
Investigators: Multicenter Trial: Investigator information is on file at AbbVie	
Study Sites: Approximately 200 sites	
Study Population: Premenopausal female subjects (aged 18 to 49 years, inclusive) with a surgical diagnosis of endometriosis within 10 years prior to screening and with moderate to severe endometriosis-associated pain.	
Number of Subjects to be Enrolled: Approximately 700	
Methodology: This Phase 3 study includes a 48-month Treatment Period and is designed to evaluate the safety and efficacy of elagolix in combination with concomitant hormonal add-back therapy (E2/NETA 1 mg/0.5 mg) in the management of endometriosis-associated pain in premenopausal women. The first 12 months of the Treatment Period will employ a randomized, double-blind, placebo-controlled design (12 months), an elagolix 200 mg BID alone arm (the first 6 months followed by elagolix 200 mg BID plus E2/NETA [1 mg/0.5 mg] QD for 6 months), and an elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD arm. The last 36 months of the Treatment Period will be open-label, such that all subjects, will receive active treatment with elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD. Protocol specific rescue analgesics will be allowed for all subjects throughout the Screening and Treatment Periods. Approximately 700 subjects will be randomly assigned on Study Day 1 in a 4:1:2 ratio of elagolix treatment in combination with E2/NETA or elagolix alone or placebo as follows: • elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (n = 400) • elagolix 200 mg BID (n = 100) • placebo (n = 200)	

Methodology (Continued):

Study Duration:

The total duration for a subject's participation in this study is approximately 51 to 74 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 consent; duration of washout depends on the type of exclusionary medication being taken).
- Screening Period – approximately 1.5 to 4 months prior to first dose of study drug.
- Treatment Period – up to 48-month treatment duration.
- Follow-Up Period – up to 12 month duration following the last dose of study drug. Subjects are expected to enter Follow-Up after Treatment Month 48, or if a subject prematurely discontinues from the Treatment Period at the time of or after Treatment Month 6.

Washout Period:

After signing the informed consent, subjects, who have been taking exclusionary medications prior to screening that require protocol specified discontinuation, must enter a Washout Period. The duration of the washout period is based on the excluded medication as described in the protocol. The following study procedures may be performed: medical, social and gynecological history (including documentation of diagnosis of endometriosis via surgical visualization or histologic diagnosis), a 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. Contraceptive counseling will be provided, and non-hormonal contraceptives dispensed, as necessary.

Methodology (Continued):

Screening Period:

Following informed consent (if Washout was not required), subjects will enter into the approximately 1.5- to 4-month Screening Period to establish eligibility based on inclusion and exclusion criteria, including the following safety baseline assessments: a dual energy x-ray absorptiometry (DXA) scan; an endometrial biopsy and transvaginal ultrasound (TVU); a Papanicolaou (Pap) test; a mammogram in subjects 40 years of age or older if one has not been performed within 3 months prior to Screening. An electronic daily 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 (no pain, mild pain, moderate pain, severe pain coded as 0 – 3); dyspareunia via a 4-point scale, plus a choice of "not applicable;" 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. During the last 35 calendar days of the Screening Period, subjects must have at least 2 days of moderate or severe DYS and 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. 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 Screening. Subjects are required to use dual non-hormonal contraception (as applicable). Contraceptive counseling will be provided and contraceptives dispensed, as necessary. Subjects will be allowed to take protocol defined analgesic rescue medication for endometriosis-associated pain. Protocol allowed analgesic rescue medication for endometriosis-associated pain will include multiple non-steroidal anti-inflammatory drug (NSAID) choices and 2 opioid choices: codeine plus acetaminophen or hydrocodone plus acetaminophen; use of other rescue analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed during this period. NSAID and opioid baseline use will be established during the Screening Period based on the subject's preference and historical use of analgesics for endometriosis-associated pain and Investigator judgment. Subjects will record use of protocol allowed analgesic rescue medications for endometriosis-associated pain in the daily e-Diary.

Treatment Period:

The Treatment Period begins on Day 1, which will occur between Cycle Days 1 to 10 from the first day of menses (defined as first day with full menstrual flow) for all subjects who meet eligibility criteria during the Screening Period.

Subjects entering the Treatment Period will visit the site monthly (28-day months) through Month 6 of the Treatment Period. After the Month 6 visit and through Month 12, on-site visits will be conducted at Treatment Months 8, 10, and 12; phone contacts will be made at other monthly timepoints. Subsequent to the Month 12 visit, on-site visits will be conducted every three months at Treatment Months 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48; phone contacts will be made at other monthly time points. Months 13 – 48 of the Treatment Period will be open-label such that all subjects (including those previously randomized to elagolix 200 mg alone or placebo) will receive active treatment with elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD. Study drug kits will be dispensed to subjects at each on-site visit with the exception of the final visit at Treatment Month 48.

Methodology (Continued):

Treatment Period (Continued):

Subjects will use the daily e-Diary to continue recording DYS and NMPP; dyspareunia, if applicable; the presence and intensity of uterine bleeding; and the use of protocol specific analgesic rescue medication for endometriosis-associated pain through Treatment Period Month 12. During Months 13 to 48, information regarding subjects' use of rescue analgesic medications for endometriosis-associated pain will be collected at monthly study visits and recorded in source documents and eCRF. At the Day 1 visit (prior to dosing) and at all monthly visits (on-site and phone contacts), site staff will administer to subjects a questionnaire assessing overall endometriosis-associated pain over a 7-day recall period (11-point NRS).

Throughout the 48-month Treatment Period, all subjects will continue to be able to take protocol specific analgesic rescue medications for endometriosis-associated pain. Use of non-protocol specific rescue analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed during the Treatment Period.

All subjects will self-administer study medication or matching placebo (through Treatment Month 12) twice daily (once in the morning and once in the evening approximately 12 hours apart), orally without regard to food or meals throughout the 48-month Treatment Period.

Subjects will complete various patient-reported outcome (PRO) questionnaires at study visits.

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 phone contact visits. A positive urine pregnancy test 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.

During the Treatment Period, blood samples will be collected for Clinical Safety Labs and vitamin D testing. In addition, blood samples will be collected for assay of serum estradiol, and to measure plasma concentrations of elagolix and norethindrone, at designated study visits. For subjects who consent, a DNA and RNA pharmacogenetic (PG) blood sample will be collected on Day 1, Month 6 and Month 12.

Vitals signs assessments will be conducted at designated time points throughout the Treatment Period. Additional safety assessments including TVUs, mammograms, Pap tests, endometrial biopsies and DXAs are completed as appropriate throughout the Treatment Period. Adverse event and concomitant medication review will be conducted at all visits (on-site and phone contacts) during the Treatment Period.

Bone Mineral Density (BMD) Assessment and Study 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, 24, 30, 36, 42, and 48. If the results of any post-baseline DXA prior to Month 48, as read by the central reader selected for the study, document 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 or BMD decrease from baseline 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.

Methodology (Continued):

Follow-Up Period:

Subjects will enter the Follow-Up Period for up to 12 months to assess bone recovery after up to 48 months of treatment. Subjects who prematurely discontinue from the study at the time of or after the Treatment Period Month 6 visit will enter the Follow-Up Period. The Follow-Up Period for the study will conclude for all subjects 30 days after the last completed Treatment Month 48 visit. 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 as defined above.

Vital signs and pregnancy testing will be performed at designated study visits. Adverse events and concomitant medication use will also be reviewed.

Central Laboratory and Central Imaging Vendors:

DXA, TVU, endometrial biopsy and clinical safety lab samples will be analyzed/evaluated using central laboratories or vendors. Assays for pharmacokinetics, pharmacodynamics and pharmacogenetics 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), that requires chronic analgesic therapy, which would interfere with the assessment of endometriosis-related 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.

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

Main Exclusion (Continued):

- Subject has any of the following:
  - Major depression or post-traumatic stress disorder (PTSD) episode 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) within the last 1 year at Screening or prior to randomization on Day 1.
- Subject has any history of osteoporosis or other metabolic bone disease or any condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, spinal hardware, severe scoliosis or weight) 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.
- 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).
- 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 randomization 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).
- 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 Products:	Elagolix Sodium 200 mg tablets Overencapsulated Estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA 1 mg/0.5 mg)
Doses:	Elagolix 200 mg BID Elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD
Mode of Administration:	Oral
Reference Therapy:	Placebo to match Elagolix; Placebo to match E2/NETA
Dose:	Placebo to match Elagolix 200 mg BID equivalent Placebo to match Elagolix 200 mg BID plus Placebo to match E2/NETA 1 mg/0.5 mg QD equivalent
Mode of Administration:	Oral
Duration of Treatment:	Subjects will receive up to 48 months of Treatment
Duration of Follow-Up:	Subjects will receive up to 12 months of Follow-Up

Criteria for Evaluation:

Efficacy:

Primary Efficacy Variables:

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; use of analgesic medication for endometriosis-associated pain will be included in the responder definition.

Secondary Efficacy Variables:

- Change from baseline in Overall Endometriosis-Associated Pain at Month 3, Month 6, and Month 12
- Change from baseline in DYS at Month 3, Month 6, and Month 12
- Change from baseline in NMPP at Month 3, Month 6, and Month 12
- Change from baseline in dyspareunia at Month 3, Month 6, and Month 12
- Change from baseline in PROMIS Fatigue Short Form 6a T-Score at Month 6 and 12

Additional Efficacy Variables:

The following efficacy variables will be collected during the treatment period:

- Proportion of responders as assessed by change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, respectively.
- Proportion of responders as assessed by change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP and dyspareunia, respectively.
- Change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.
- Change from Baseline in analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary monthly.

Criteria for Evaluation (Continued):

Efficacy (Continued):

- Proportion of analgesic use responders monthly (based only on reduction of rescue analgesics used).
- Monthly response in the PGIC and overall endometriosis-associated pain questionnaire.
- Change from baseline for each of six domains of EHP-30 questionnaire scores.
- Change from baseline for the EuroQoL-5D (EQ-5D-5L).
- Change from baseline for the WPAI:SHP.
- HCRU at each scheduled assessment.
- Change from baseline for the PROMIS Fatigue short Form 6A T-Score.

Safety Assessments:

Safety assessment will include BMD measurements including Z- and T-scores and percent change from baseline as measured by DXA at Months 6, 12, 18, 24, 30, 36, 42, and 48 of the Treatment Period. Other safety evaluations will include physical examinations, mammograms, Adverse Events (AEs), clinical laboratory tests (including hematology, chemistry, urinalysis, and lipid panel), the C-SSRS, vital sign measurements (including electrocardiogram). Endometrial assessments will include TVU and endometrial biopsy.

Statistical Methods:

Efficacy:

All subjects who receive at least 1 dose of study medication will be included in the efficacy analyses. For each of the co-primary endpoints, the criterion for defining a subject as a pain responder at Month 6 of the Treatment Period will be a reduction of 'X' or greater from Baseline in pain as well as no increased rescue analgesic use for endometriosis-associated pain. The threshold X will be determined based on ROC analysis at Month 6 using the Month 6 PGIC as an anchor. The use of protocol specified rescue analgesics at Month 6 of the Treatment Period for endometriosis-associated pain will be included in the responder definition. The primary analysis of the co-primary endpoint will be based on a logistic regression model including treatment as the main factor and baseline pain scores as a covariate and the elagolix 200 mg BID plus E2/NETA dose will be compared to placebo.

Analysis details for Months 1 – 12 and Months 13 – 48 of the treatment period will be specified in the statistical analysis plan (SAP). No statistical tests will be performed following the 12-month placebo-controlled portion of the 48-month Treatment Period. Data from subjects randomized to the elagolix 200 mg BID alone will be summarized separately from subjects randomized to the elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD arm. Unless otherwise specified, no statistical tests will be performed to evaluate potential differences between the two elagolix dose groups.

The mean change from baseline in key secondary endpoints will be analyzed using a mixed-effects model with repeated measures. Key secondary endpoints will be assessed at Month 3, Month 6 or Month 12. Other efficacy endpoints and analyses will be defined in the SAP.

For subjects randomized to placebo in the first 12 months of the treatment period, baseline will be re-set to the data collected the month prior to the first dose of elagolix in Months 13 – 48 of the treatment period. For subjects randomized to either one of the elagolix treatment groups, baseline for these subjects will refer to the baseline prior to the first dose of elagolix at the time of randomization.

Statistical Methods (Continued):

BMD Assessments:

The key BMD comparisons are in lumbar spine at Month 6 and Month 12. Secondary BMD endpoints include total hip and femoral neck. The elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD dose will be compared to placebo at Months 6 and 12 and will be compared to Elagolix 200 mg BID alone at Month 6 based on percent change from baseline. Percent change in BMD from baseline values, as well as Z-scores and T-scores at all time points will also be summarized. Analysis details will be provided in the SAP.

Safety Assessments:

All subjects who receive at least 1 dose of study medication will be included in the safety analyses. Hematology, chemistry (including lipid panel), urinalysis, vital signs, endometrial assessments and uterine bleeding variables will be summarized. Changes from Baseline to each Treatment Period visit during the first 12 months of treatment will be analyzed using an ANOVA or ANCOVA model as appropriate as specified in the SAP.

Safety analysis for Months 1 – 12 and Months 13 – 48 of the treatment period will be specified in the statistical analysis plan. No statistical tests will be performed to evaluate potential differences between dose groups following the 12-month placebo-controlled portion of the 48-month Treatment Period.

Safety data from subjects randomized to the elagolix 200 mg BID alone treatment group will be summarized separately from subjects randomized to the elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD arm.

Other safety analyses will be pre-specified in the SAP.

Pharmacokinetic:

Exposures of elagolix and norethindrone will be summarized and elagolix concentrations may be used to develop a population pharmacokinetic model. Additional parameters may be calculated if useful for the interpretation of the data.

Pharmacodynamic:

Concentrations of estradiol (E2) will be obtained throughout the Treatment Period. Additional pharmacodynamic parameters may be calculated if useful in the interpretation of the data.

1.3 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
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP3A	Cytochrome P450 3A
DNA	Deoxyribonucleic acid
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
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
ORT	Opioid Risk Tool
Pap	Papanicolaou
PD	Premature Discontinuation
PG	Pharmacogenetic
PGIC	Patient Global Impression of Change
PK	Pharmacokinetic
POR	Proof of Receipt
PRO	Patient Reported Outcome
QD	Once a day
RBC	Red Blood Cell
RNA	Ribonucleic acid
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
mITT	Modified intent to treat
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

Randomization	Randomization at the end of the Screening Period on Study Day 1.
E2/NETA	1 mg E2/0.5 mg NETA
Month	A month is defined as 28 days.

2.0 Table of Contents

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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 is an oral, nonpeptide gonadotropin releasing hormone (GnRH) antagonist that is being developed by AbbVie for women with heavy menstrual bleeding associated with uterine fibroids and has been approved for the management of moderate to severe pain associated with endometriosis.

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.

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 endometriosis studies, elagolix met its primary efficacy endpoints of a statistically significant and clinically meaningful decrease in dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) at 3 months with continued efficacy at 6 months for both the 150 mg QD and 200 mg BID dose levels. The 150 mg QD dose demonstrated efficacy in 3 of 7 key ranked secondary outcome measures while the 200 mg BID dose showed a statistically significant improvement in all 7 key ranked secondary outcome measures. Also 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) would likely 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. Although there is no evidence of fetal abnormalities in preclinical studies, there have been 2 cases of congenital malformations in clinical studies of elagolix to date. Although not thought to be related to elagolix, the true relationship is unknown. Elagolix should not be used in women who are pregnant or trying to become pregnant because, elagolix, like most GnRH analogues, affects the reproductive hormonal milieu. Information regarding contraception counseling and pregnancy testing is provided in Section 5.2.4.

3.3 Differences Statement

This Phase 3 study will evaluate the safety and efficacy of the elagolix 200 mg BID dose in combination with hormonal add-back therapy in 18 to 49 year old premenopausal women with moderate to severe endometriosis-associated pain over a 4 year period. The objective is to generate safety and efficacy data that would support a longer duration of

use of this regimen for the management of endometriosis-associated pain than the Phase 3 registration program.

Efficacy data from the ongoing 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. Also consistent with E2 suppression and 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 loss, which is the hypothesis being tested in this study. The current study evaluates the safety and efficacy of the elagolix 200 mg BID dose in combination with estrogen/progestin hormonal add-back therapy for a 48 month treatment period. All subjects will be followed for up to 12 months during the Follow-up Period.

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 4,800 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:

- Assess the safety and efficacy of elagolix 200 mg administered twice daily (BID) in combination with estradiol 1 mg/0.5 mg norethindrone acetate (E2/NETA 1 mg/0.5 mg) QD compared to placebo at 6 months and 12 months;
- Assess the effect of elagolix 200 mg BID in combination with E2/NETA (1 mg/0.5 mg) QD on bone mineral density (BMD) compared to elagolix 200 mg BID alone at 6 months and compared to placebo at 6 months and 12 months;
- Evaluate the continued safety and efficacy of elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD for up to 48 months in premenopausal women with moderate to severe endometriosis-associated pain

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This Phase 3 study includes a 48-month Treatment Period and is designed to evaluate the safety and efficacy of elagolix in combination with concomitant hormonal add-back therapy (E2/NETA 1 mg/0.5 mg) in the management of endometriosis-associated pain in premenopausal women. The first 12 months of the Treatment Period will employ a randomized, double-blind, placebo-controlled design (12 months), an elagolix 200 mg BID alone arm (the first 6 months followed by elagolix 200 mg BID plus E2/NETA [1 mg/0.5 mg] QD), and an elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD arm. The remaining 36 months of the Treatment Period will be open-label, such that all subjects will receive elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD.

Approximately 700 subjects will be randomly assigned on Study Day 1 in a 4:1:2 ratio as follows:

- elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (n = 400)
- elagolix 200 mg BID (n = 100)

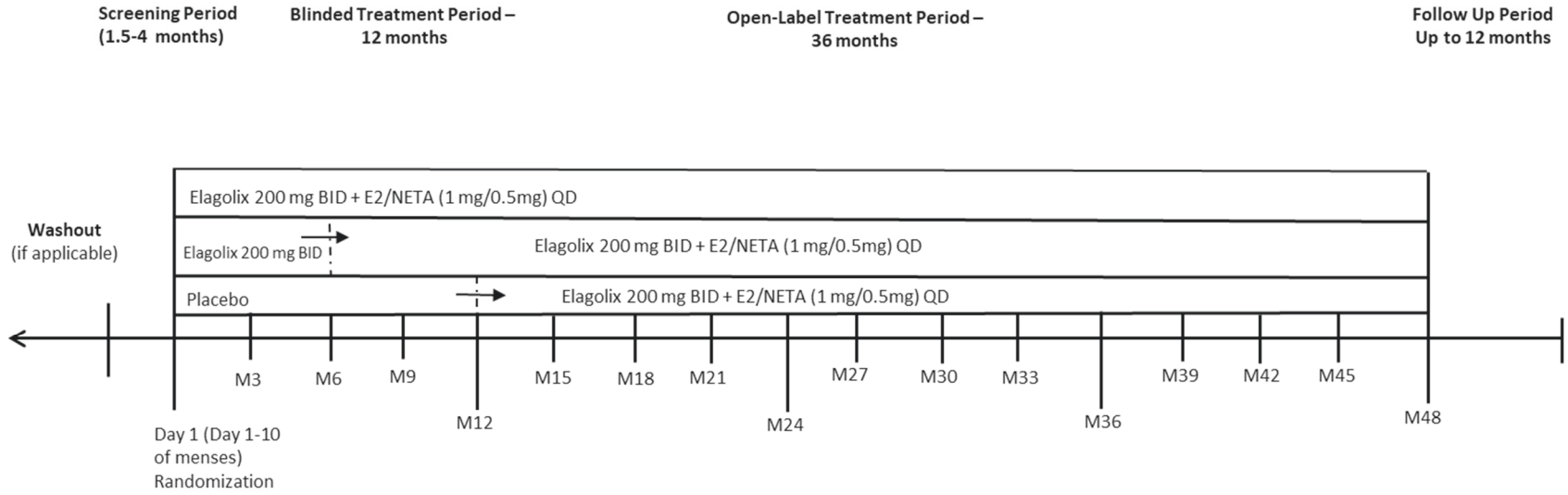
- placebo (n = 200)

The study was designed to enroll approximately 700 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled. The total duration for a subject's participation in this study is approximately 51 to 74 months, consisting of the following 4 study periods:

- Washout Period – up to 10 months prior to Screening (only applicable if subject is taking exclusionary medication at the time of consent; duration of washout depends on the type of exclusionary medication being taken)
- Screening Period – approximately 1.5 to 4 months prior to first dose of study drug
- Treatment Period – up to 48-month treatment duration
- Follow-Up Period – up to 12 months duration following the last dose of study drug. Subjects are expected to enter Follow-Up after completing Treatment Month 48, or if a subject prematurely discontinues from the Treatment Period at the time of or after Treatment Month 6.

The study schematic is shown below in Figure 1:

Figure 1. Study Schematic



Washout Period

Following informed consent, subjects, who are or were taking exclusionary hormonal/anti-hormonal medications prior to screening that require discontinuation (washout), must enter a Washout Period. The duration of the required washout period is based on the excluded medication that the subject is or was taking. Additional details about washout intervals for exclusionary medication is provided in Section 5.2.3.1. Study procedures to be performed during the Washout Period are specified in Appendix C, Study Activities and described in Section 5.3.1.1. 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

Subjects who do not require washout will enter directly into the Screening Period (approximately 1.5 to 4 months) and will provide written informed consent before any study related procedures are performed. Subjects will undergo screening procedures as specified in Appendix C, Study Activities and described in Section 5.3.1.1, to establish eligibility based on inclusion and exclusion criteria including the following safety assessments:

- a dual energy x-ray absorptiometry (DXA) scan to document baseline bone mineral density (BMD)
- a transvaginal ultrasound (TVU) to rule out any exclusionary gynecological disorders such as ovarian cysts, large fibroids, endometrial polyps
- an endometrial biopsy to rule out other endometrial pathology
- a Papanicolaou (Pap) test in subjects ≥ 21 years of age, to rule out significant cervical/gynecological pathology
- a mammogram in subjects 40 years of age or older if one has not been performed within 3 months prior to the time of entry into Screening

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

- endometriosis-associated pain (dysmenorrhea [DYS] or non-menstrual pelvic pain [NMPP]) using the 4 point Endometriosis Daily Pain Impact Diary scale (no pain, mild pain, moderate pain, severe pain coded as 0 – 3)
- dyspareunia via a 4-point scale (no pain, mild pain, moderate pain, severe pain coded as 0 – 3, and not applicable)
- the presence of uterine bleeding (menstrual period and other uterine bleeding) and intensity of bleeding (spotting, light, medium, heavy)

A minimum of 45 days of daily e-Diary entries are required to be completed during the Screening Period. During the last 35 calendar days of the Screening Period, subjects must have at least 2 days of moderate or severe DYS and 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 with an average NMPP score of at least 0.5. 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 Screening. Subjects are required to use appropriate non-hormonal contraception throughout the Screening Period. Contraceptive counseling will be provided and contraceptives dispensed, as necessary. Subjects will be allowed to take protocol allowed analgesic rescue medication for endometriosis-associated pain which includes multiple NSAID choices and opioid choices. Use of other rescue analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed. NSAID and opioid baseline use will be established during the Screening Period based on the subject's preference and historical use of analgesics for endometriosis-associated pain and Investigator judgment. Subjects will record use of protocol allowed analgesic rescue medications for endometriosis-associated pain in the daily e-Diary. Sites will record the use of protocol-allowed rescue analgesics in the source documents and eCRF.

Subjects who have signed 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. Subjects who screen failed due to ediary pain criteria, Screening DXA results, or C-SSRS criteria cannot be re-screened.

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. Subjects may only re-screen once.

Urine and serum pregnancy tests must be repeated upon re-screen. The following screening procedures do not need to be repeated upon re-screen:

- Endometrial biopsy, PAP and/or mammogram if completed within 12 months for the study,
- DXA, TVU, Clinical/Safety Labs, Vitamin D Testing, Hepatitis/HIV Screen, if completed within 4 months for the study.

Treatment Period

The Treatment Period begins on Day 1, which should occur between Cycle Days 1 to 10 of the subject's menstrual cycle (Cycle Day 1 is defined as the first day with full menstrual flow), for all subjects following determination of eligibility during the Screening Period. Randomizations beyond Cycle Day 10 of the subject's menstrual cycle must be discussed with the AbbVie Therapeutic Area Medical Director (TA MD) prior to randomizing the subject and will be evaluated on a case by case basis, including whether additional procedures are required.

On Day 1 of the Treatment Period, subjects will be randomly assigned (in a 4:1:2 ratio) to receive either elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (n = 400), elagolix 200 mg BID alone (n = 100), or placebo (n = 200). The first dose of study drug will be administered at the study site on Day 1. Thereafter, subjects will self-administer study medication or matching placebo twice daily (once in the morning and once in the evening, approximately 12 hours apart) orally without regard to food or meals throughout the 48-month Treatment Period. Subjects will visit the site monthly (28-day months) through Month 6 of the Treatment Period. After the Month 6 visit and through Month 12, on-site

visits will be conducted at Treatment Months 8, 10, and 12; phone contacts will be made at Treatment Months 7, 9, and 11.

Months 13 – 48 of the Treatment Period will be open-label such that all subjects (including those previously randomized to elagolix 200 mg BID alone or placebo) will receive active treatment with elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD. On-site visits will be conducted at Months 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48; phone contacts will be made at Months 13 – 14, 16 – 17, 19 – 20, 22 – 23, 25 – 26, 28 – 29, 31 – 32, 34 – 35, 37 – 38, 40 – 41, 43 – 44, and 46 – 47.

Study drug kits will be dispensed to subjects at each on-site visit with the exception of the final visit at Treatment Month 48. Subjects randomized to elagolix plus E2/NETA on Day 1 of the Treatment Period will continue with the same dosing regimen (dose and frequency) throughout the entire Treatment Period; subjects randomized to elagolix 200 mg BID alone during the first 6 months will be reassigned to receive elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD for the remainder of the Treatment Period (Months 7 – 48); subjects randomized to placebo will be reassigned at Treatment Month 12 to receive elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD for the remainder of the Treatment Period. All subjects will know they are receiving elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD during Months 13 – 48.

Through Treatment Month 12, subjects will use the daily e-Diary to continue recording:

- endometriosis-associated pain (DYS and NMPP via the 4 point Endometriosis Daily Pain Impact Scale) (no pain, mild pain, moderate pain, severe pain coded as 0 – 3)
- dyspareunia via a 4-point scale (no pain, mild pain, moderate pain, severe pain coded as 0 – 3, and not applicable)
- the presence of uterine bleeding (menstrual period and other uterine bleeding) and intensity of bleeding (spotting, light, medium, heavy)
- use of protocol specific analgesic rescue medications for endometriosis-associated pain

At the Day 1 visit (prior to dosing) and at all monthly visits during the Treatment Period (on-site and phone contacts), site staff will administer to subjects the overall endometriosis-associated pain questionnaire, an 11-point numeric rating scale (NRS).

Information regarding the use of rescue analgesic medications for endometriosis-associated pain will be collected at monthly study visits and recorded in source documents and eCRF.

At select study visits, subjects will be asked to complete various patient-reported outcome (PRO) questionnaires, including a Patient Global Impression of Change (PGIC). Vital signs assessments will be conducted at designated time points. Additional safety assessments including mammograms, TVUs, Pap tests, endometrial biopsies, and DXAs are completed as appropriate throughout the Treatment Period.

Blood samples for clinical safety labs and vitamin D testing and will be obtained. In addition, blood samples will be collected for assay of serum estradiol prior to dosing on Day 1 and at designated study visits, and to measure plasma concentrations of elagolix and norethindrone at designated study visits. For subjects who consent, 3 separate DNA (Deoxyribonucleic acid) and RNA (Ribonucleic acid) pharmacogenetic (PG) blood samples and 2 endometrial samples will be collected. Pregnancy tests will be performed at each monthly 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 phone contact visits. Subjects will be counseled at each visit on consistent, appropriate and effective forms of dual non-hormonal contraception to promote pregnancy prevention. A positive urine pregnancy test must be confirmed with a serum pregnancy test. A positive serum pregnancy test at any time will necessitate discontinuation from the Treatment Period.

Additional detail regarding study procedures during the Treatment Period is provided in Section 5.3.1.1 and Appendix C, Study Activities.

Follow-Up Period

Subjects will enter the Follow-Up Period for up to 12 months to assess bone recovery after up to 48 months of treatment. Subjects who prematurely discontinue from the study at the time of or after the Treatment Period Month 6 visit will enter the Follow-Up Period. The Follow-Up Period for the study should conclude for all subjects approximately 30 days after the last completed Treatment Month 48 visit.

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 on-site visits.

Additional detail regarding study procedures during the Follow-Up Period is provided in Section 5.3.1.1 and 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 must have 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; periodic abstinence is not acceptable and requires use of dual contraception.
   - Subject had a bilateral tubal ligation or bilateral tubal occlusion 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 ≥ 40 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 3 or equivalent).

8. Prior to Study Day 1, subject must have 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 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.

Rationale for Inclusion Criteria

1	This is standard criterion in accordance with harmonized Good Clinical Practice (GCP)
2 – 4, 8 – 10	These criteria were selected to ensure an appropriate subject population of premenopausal women with moderate to severe endometriosis-associated pain
5, 6	The impact of elagolix on pregnancies or breastfed infants is unknown and there is a possible risk of miscarriage due to changes in hormone levels; therefore, these criteria ensure pregnant women are not enrolled into the study and adequate precautions are taken to avoid pregnancy during study participation
7	To ensure general good health and the safety of subjects

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 74 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 ≥ 21 years of age at Screening (or age at which Pap smears are routinely performed according to local guidelines) 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, or these preparations (e.g., E2/NETA) are contraindicated for medical reasons.
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 all 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 any of the following:

- Major depression or a post-traumatic stress disorder (PTSD) episode 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) within the last 1 year at Screening or Day 1, prior to randomization.

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 randomization 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.

27. Subject was previously enrolled (randomized) in an elagolix study 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.

30. Subject scores an 8 or higher on the Opioid Risk Tool at Screening.

Rationale for Exclusion Criteria

4, 5, 12	These criteria were selected to ensure an adequate subject population of premenopausal women with moderate to severe endometriosis pain and no significant gynecological disorders
3, 6 – 9, 14 – 26, 30	These are standard criteria selected to ensure general good health and the safety of the subjects
1, 2	The impact of elagolix on pregnancies or breastfed infants is unknown and there is a possible risk of miscarriage due to changes in hormone levels; therefore, these criteria ensure pregnant women are not enrolled into the study and adequate precautions are taken to avoid pregnancy during study participation
27, 28	These criteria were selected to avoid bias for the evaluation of efficacy and safety by prior participation in an elagolix or similar study

10, 11, 13, 29	These criteria were selected to ensure that efficacy can be adequately assessed

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 enrollment, 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.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

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 discretion.

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 contraceptive 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 your AbbVie TA MD.

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

Therapy	Minimum Interval for Washout* (Prior to Initial Screening Visit)	Number of Menses Required AFTER Completion of Washout Period (Prior to Initial Screening Visit)
Medroxy progesterone acetate injection (Depo-Provera®; Sayana®)	10 months from injection	2 menses
GnRH agonist 3 month depot (Lupron Depot® 11.25 mg), goserelin acetate (Zoladex®, 10.8 mg)	6 months from injection	1 menses
Synarel® (Nasal Spray), Nafarelin acetate, GnRH agonist – 1 month depot (including Lupron Depot® 3.75 mg), goserelin acetate (Zoladex® 3.6 mg)	4 months	1 menses
GnRH antagonist	3 months	1 menses
Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate, Vilaprisan)		
Danazol (Cyclomen®)		
Aromatase inhibitors		
Oral contraceptives**	1 month	1 menses
Oral, transdermal or intravaginal estrogen preparations		
Oral, intravaginal or transdermal progesterone/progestin preparations***, including tibolone		
Hormonal and Non-Hormonal IUD, sub-dermal progestin implant (e.g., Nexplanon®)	1 month after removal	1 menses
NuvaRing®		

* This is the minimum washout; however, subjects may not enter Screening until at least 1 menses 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 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 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 significantly 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 agonist	Leuprolide acetate (Lupron®)
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:	GnRH agonist: nafarelin acetate (Synarel®), goserelin acetate (Zoladex®) Danazol (Danocrine®, Cyclomen®) Medroxyprogesterone Acetate (Depo-Provera®, Provera®) 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 Screening and Treatment Periods	
Immediate Release (IR) Opioid Analgesics, such as:	Oxymorphone Hydromorphone Morphine Buprenorphine *Except for short-term use as noted below.*
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.*
Prohibited 1 Month Prior to Day 1 and During the Treatment Period	
Moderate or strong CYP3A[7] Inducers, such as:	**Moderate Inducers:** Bosentan Efavirenz Etravirine Modafinil **Strong Inducers:** St. John's Wort Rifampin Carbamazepine Phenytoin Mitotane 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.*
Cannabinoids (including marijuana use)	
Other Teratogens, such as:	Topiramate, Accutane® and other oral retinoids
GnRH antagonists (including investigational ones), such as:	Orilissa®, relugolix

Any analgesic medications used to specifically treat endometriosis-associated pain, with the exception of 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 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 48 month Treatment Period is allowed during a subject's participation. If the subject requires more than 2 weeks duration per occurrence or more than 6 weeks (total of 42 days) over the 48 month Treatment Period, their continued participation in the study must be reviewed with the AbbVie TA 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 MD. If

there are any questions regarding prior or concomitant therapy, please contact the AbbVie TA MD.

5.2.3.4 Rescue Therapy

The protocol-allowed analgesic rescue therapies for endometriosis-associated pain are presented in Table 3. Investigators must prescribe a specific analgesic rescue medication from each medication class for subjects at the time of entry into the Screening Period. The choice of which protocol-allowed rescue NSAID and opioid prescribed per protocol should take into consideration the subject's preference and/or historical use of analgesics.

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 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.

During the Screening and Treatment Periods, 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. If an abuse pattern is detected, the subject's continued participation in the study should be evaluated by the Investigator.

Subjects will record use of the protocol-specific rescue analgesic medications taken for endometriosis-associated pain daily in the eDiary during Screening and the first 12 months of the Treatment Period. This will include specific information for the allowable rescue analgesics, including total number of pills/tablets taken for each category of rescue analgesic medication within a 24-hour period.

Prophylactic use of protocol-specific rescue analgesic medications or other analgesic medications for endometriosis-associated pain is not allowed. Also, use of any other analgesic for treatment of endometriosis-associated pain is prohibited during the study (from the start of the Screening Period through the 48-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 MD. 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

* Total daily dose 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.

*** Combination with or without caffeine is permitted.

5.2.4 Contraception Recommendations and Pregnancy Testing

Contraception Counseling/Dispensing Contraceptives

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 or bilateral tubal occlusion) 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. Subjects may begin the use of hormonal contraception (e.g., oral or IUD) after completion of the Follow-Up Month 1 visit provided that the subject has a documented menstrual period after the Treatment Period and prior to that visit.

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 or bilateral tubal occlusion 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 is not acceptable and 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 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, if needed, including proper diaphragm use.
   - The site will provide contraceptives and other supplies (e.g., lubricants) to subjects throughout the Washout (if applicable), Screening, and Treatment Periods, as needed. If necessary, the subject may obtain protocol-allowed contraceptives apart from the study site. In this situation, the study site still must document the form/type of contraceptives obtained, and subjects' attestation of consistent use of these non-hormonal contraceptives throughout study participation.
   - 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 at the time of consent, and subsequently in a stand-alone attestation form at all on-site study visits 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®), attestation is only required to be collected once during the study prior to randomization, 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.
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 phone 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 randomization. Prior to performing an endometrial biopsy, the subject must have a confirmed negative urine pregnancy test. In addition, 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., phone contact visits and prior to certain study procedures). Subjects will self-administer the tests and report the results to the site during phone 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 6.1.6). 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 randomization 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, Pharmacogenetic 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 Study 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) and adverse event information (Section 6.0). All study data will be recorded on the eCRF 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 (randomization). For procedures repeated during the Screening Period (as allowed per protocol or at the discretion of the AbbVie TA MD), the procedure performed closest to dosing will serve as a baseline for clinical assessment.

Study procedures during the Treatment and Follow-Up Periods may be performed within the visit windows specified in the applicable sections of the protocol. 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 projected date. However, the TVU, DXA scan, PAP test and endometrial biopsy may be performed within approximately ± 15 days around the 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 MD 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 MD 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. Pharmacogenetic (PG) testing is optional and a subject must be provided a separate informed consent form for this blood and endometrial biopsy sample collection. 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 randomize 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. Subjects who re-screen will be required to sign a new informed consent form.

Medical/Social History

A complete medical history, including documentation of any clinically significant medical conditions and medications, and history of tobacco and alcohol use, and licit/illicit drug abuse 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) and will serve as the baseline for clinical assessment.

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 examination are outlined in the Study Activities Table in Appendix C.

Clinically significant physical examination findings prior to randomization will be recorded as medical 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 (External Genitalia, Pelvic and Breast) 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 and pelvic 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 40 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 MD 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, 2 or 3 (via mammogram or other mode of imaging) as outlined in Appendix D will be eligible for randomization on Day 1. Subjects with an abnormal mammogram or BI-RADS Classifications 4, 5, or 6 will not be eligible for the study. Subjects not eligible for the study should continue with recommended mammography testing outside of the protocol per local guidelines and standard of care during the study.

During the Treatment Period, mammograms will also be performed for subjects who are 40 years of age or older at the time of the scheduled study visit at Month 12, Month 24, Month 36, and Month 48 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 mammogram within approximately 6 months prior to the PD visit). Mammograms may be performed within approximately ± 15 days of the scheduled corresponding visit. All mammograms will be read locally. If a subject has a clinically significant mammogram finding in the opinion of the investigator, or BI-RADS Classifications 4, 5, or 6, or there is a recommendation for additional testing, the AbbVie TA MD should be notified for additional guidance and approval.

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 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 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 ideally 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, Month 24, Month 36, and Month 48 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 6 months 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, Month 24, Month 36, and Month 48 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 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 Core Lab (central reader). The DXA technologist/radiologist or designee for each investigative site should electronically submit the subject's DXA images to the central reader for review and analysis within 3 business days following acquisition. Subject eligibility and treatment management will be made based on the central reader review. Sites will receive reports from the central reader detailing the results (including Z-scores for subjects < 40 years of age or T-scores for subjects ≥ 40 years of age, BMD measurements and % change from baseline, as applicable measurements) 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 reader that will be provided to all study sites. Site training and qualifications, including assessment of instruments, will be evaluated/approved by the central reader, 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 randomization 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, 24, 30, 36, 42, and 48 and will be submitted to the central reader for review and analysis. The central reader 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, 24, 30, 36, 42, and 48 is ± 15 days around the respective study visit.

If the results of any post-baseline DXA prior to Month 48, as read by the central reader 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 OR
- a BMD decrease from baseline of > 8% in the lumbar spine, total hip or femoral neck

If the BMD percent change from baseline of any post-baseline DXA prior to Month 48 cannot be provided by the central reader (i.e., due to scanner changes), then the TA MD must be consulted to confirm if the subject can continue study drug dosing. 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 any time at the time of or after the Treatment Month 6 visit, or if one was not performed within approximately 6 months of the PD 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, BMD decrease from baseline of > 8% in any region, or TA MD assessment, 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., 30 days after the last completed Treatment Month 48 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. Pre-medication for the endometrial biopsy procedure is allowable, e.g., 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. The Investigator should write a brief procedure note in the source documentation noting the depth of placement of the Pipelle during the procedure. If an endometrial biopsy cannot be performed because of anatomical reasons, the AbbVie TA MD should be consulted for further guidance.

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

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 randomization on Day 1. However, if the repeat sample is deemed insufficient by the central laboratory, the AbbVie TA MD should be consulted regarding eligibility.

If an endometrial biopsy has been performed within a year prior to entry into Screening and is not abnormal (hyperplasia or worse) then endometrial biopsy does not need to be repeated prior to randomization. Biopsy results must be obtained and reviewed by the Investigator to ensure eligibility criteria are met before the subject can be randomized on Day 1. Results from the historical biopsy (i.e., results used to determine eligibility) will be entered into the eCRF.

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 randomization 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 randomization.

The endometrial biopsies required during the Treatment period may be performed within approximately ± 15 days around the scheduled study visit. At Treatment Month 12, 24, or 36 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.

An endometrial biopsy is not required during the Treatment Period if the TVU findings at Treatment Month 12, 24, 36, 48, or Premature Discontinuation indicate an endometrial thickness < 4 mm. An endometrial biopsy is also not required at Premature Discontinuation if one was performed within approximately six months of the subject discontinuing from the study. If the TVU findings at any visit time point during the Treatment Period indicate an endometrial thickness ≥ 4 mm, then the subject must have an endometrial biopsy performed and the AbbVie TA MD must be notified to assess the subject's continued eligibility. Data from both procedures may be taken into consideration by the AbbVie TA MD when assessing the subject's continued eligibility.

Pap Test

Pap test will be performed on subjects 21 years of age or older 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. 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 randomization on Day 1.

Subjects with following finding will be eligible for randomization 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 randomization 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 MD to determine if the subject may remain in screening and can be eligible for randomization.

During the Treatment Period, if the Pap Test performed at Month 24 and/or Month 48 indicates a clinically significant finding in the opinion of the investigator and requires additional testing (e.g., colposcopy or biopsy) as follow-up, the AbbVie TA MD should

be notified for additional guidance and approval. A Pap Test is not required at PD if one was performed within approximately six months prior to the PD visit.

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
Pregnancy Test		**Lipid Panel (After Minimum 8-Hour Fast)**
Serum pregnancy		Low-density Lipoprotein (LDL) cholesterol High-density Lipoprotein (HDL) cholesterol Total cholesterol Triglycerides
		Endocrine Panel
		Follicle-stimulating hormone (FSH) Reflexive Thyroid Stimulating Hormone (TSH)

Laboratory samples indicated in Table 4 will be assessed using a 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 source documents and 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-randomization 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 6.0).

All screening laboratory results must be reviewed prior to randomization, 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 randomization. Subjects will not be randomized 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 source documents and the lab requisition should be marked to indicate that the sample was obtained under non-fasting conditions.

Endocrine Panel

The endocrine panel 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. 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 (eDiary)

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 12. The eDiary 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 throughout the Screening Period through Month 12 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 12, 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 12 study visit or at the Premature Discontinuation visit (if prior to Treatment Month 12).

Subjects will use the e-Diary to record assessments of DYS, NMPP, dyspareunia and uterine bleeding, as well as the use of protocol-allowed rescue analgesic medications for endometriosis-associated pain. Scores from these daily assessments collected during Screening will be used to evaluate subject eligibility for the study prior to randomization on Day 1. These assessments will continue to be completed daily through Month 12 of the Treatment Period or until a subject prematurely discontinues from the Treatment Period (if they discontinue prior to Treatment Month 12).

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.

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 12. Subjects will report whether they have taken pain medication documenting the total number of pills taken within each class (NSAIDs or opioids) of protocol-allowed rescue analgesic during the last 24-hour period.

The use of protocol-allowed rescue analgesic medications taken during the Screening and Treatment Periods will be recorded by site staff in the subjects' source documents and eCRF.

Patient Reported Outcomes (PRO) and Outcomes Rating Scales

Prior to the start of the study, detailed instructions and training for study site staff administering these rating scales will be provided by AbbVie and/or its designee. The objective of this training is to establish uniformity across sites in administration of these rating instruments. 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), as applicable.

Overall Endometriosis-Associated Pain

Beginning at Day 1 of the Treatment Period and at all monthly visits during the Treatment Period (on-site and phone 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 at the time of the visit.

Endometriosis Health Profile-30 (EHP-30)[8]

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™)[9,10]

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 also 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)[11]

The WPAI:SHP questionnaire is a standardized, self-administered questionnaire about work and activity impairment due to health problems. The WPAI-SHP will be adapted to inquire about work and activity impairment due to endometriosis-associated pain. Subjects will complete this questionnaire on an electronic tablet device.

PROMIS Fatigue Short Form 6a[12]

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: very much improved, much improved, minimally improved, not changed, minimally worse, much worse or very much worse. Subjects will complete this questionnaire on an electronic tablet device.

Additional Questionnaires

BMD Risk Factor Assessment Questionnaire (Appendix G)

Information will be obtained to help identify risk factors potentially associated with changes in bone mineral density (BMD) at study visits as outlined in Appendix C. Subjects will be asked about modifiable and non-modifiable risk factors, e.g., smoking and alcohol use, exercise habits, and dietary intake of calcium. Information about exercise habits will be collected via the IPAQ.[13] As applicable, site staff will elicit subject responses and record appropriately or subjects will be asked to enter their responses via an electronic tablet device.

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 (prior to randomization). The

C-SSRS, Since Last Visit questionnaire should be administered by site staff during the Treatment Period as indicated in Appendix C.

During Screening or at the Day 1 visit, prior to randomization, any subject noted to have suicidal ideation within the last year, either via answering "yes" to question 4 and/or question 5 to the suicidal ideation portion of the C-SSRS, or via clinical interview, is not eligible for randomization. Following randomization, if the subject expresses suicidal ideation on the C-SSRS or via clinical interview at any time during the study, the Investigator should immediately notify the AbbVie TA MD. Appropriate steps will be taken to protect the subject (including possible discontinuation from the study and referral for appropriate psychiatric care). The C-SSRS administered at the Day 1 visit will serve as the baseline for clinical assessment.

Opioid Risk Tool (ORT)

The Opioid Risk Tool (ORT) is a self-report screening tool designed to assess risk for opioid abuse among individuals prescribed opioids for treatment of chronic pain. The ORT will be administered to subjects and scored by site staff at the Screening visit. Subjects with a score of 8 or higher are not eligible for randomization.

Health Care Resource Utilization (HCRU)

The Health Care Resource Utilization tool captures subject visits to non-study Health Care Practitioners prior to randomization and during the Treatment Period. On Day 1, subjects will be asked to provide information on any visits to non-study Health Care Practitioners for non-study health visits over the last 4 weeks. At subsequent Treatment Period study visits (on-site and phone 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 (Treatment Month 1 to Treatment Month 24) or in the last six months (Treatment Month 25 to Treatment Month 48). The subject's responses will be recorded on the HCRU worksheet by the site staff.

Post-Treatment Assessment of Menstruation

Subjects will be asked about post-treatment to menses using the Return to Menses Questionnaire (Appendix H) 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 returned to menses, site staff will continue to assess return to menstruation and repeat the questionnaire at subsequent follow-up visits, as applicable. The date when menses returned will be documented in the source documents and eCRFs.

Assignment of Subject Numbers

The site will contact the Interactive Response Technology (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 randomized 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.

Randomization/Study Drug Kit Assignment

Subjects are to be randomized between Cycle Days 1 – 10 of her menstrual cycle (Cycle Day 1 is defined as the first day with full menstrual flow); however, randomizations beyond Day 10 of the subject's menstrual cycle must be discussed with the AbbVie TA MD prior to randomizing the subject and will be evaluated on a case by case basis, including whether additional procedures are required.

At the Day 1 visit, eligible subjects will be randomly assigned to 1 of 3 treatment groups by using IRT and entering the same subject number received during Screening or Washout. 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. In order to maintain the blind through Treatment Month 12 for all subjects, at Month 6 subjects randomized to elagolix 200 mg BID alone on Day 1 will be re-assigned (in a blinded manner) to the elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD treatment group via IRT and continue with this dosing regimen throughout the remainder of the Treatment Period (Months 7 – 48).

During the Treatment Period, sites will register each on-site monthly visit in IRT in order to obtain the appropriate amount of scheduled re-supply of study drug to dispense to each subject. (For example, the site will register the Treatment Month 8 visit in IRT in order to have 2 months' worth of study drug dispensed until the next on-site study visit at Treatment Month 10).

5.3.1.2 Collection and Handling of Exploratory Research Samples

Exploratory Research Samples

Subjects will have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

AbbVie (or people or companies working with AbbVie) will store the exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on elagolix (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent (via a separate consent document) for exploratory research samples is discussed in Section 9.3.

Samples for Pharmacogenetic Exploratory Research

Two optional whole blood samples, one for DNA and a second for RNA will be collected on Day 1, Month 6, Month 12 and Premature Discontinuation Visit (if applicable) from

each subject who consents to provide samples for exploratory research. An endometrial sample for pharmacogenetic testing will be collected during Screening and at Month 12 for each subject who consents to provide samples for exploratory research.

Samples will be shipped frozen to AbbVie or a designated laboratory for DNA and RNA extraction and long-term storage. Instructions for the preparation and shipment of the pharmacogenetic exploratory research samples will be provided in a study-specific laboratory manual.

5.3.1.3 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 7 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 date and time of collection will be recorded in the source documentation. The Day 1 sample will be obtained pre-dose; samples collected at all other visits can be drawn at any time during the visit.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood Samples for Elagolix and Norethindrone Assay

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.

Samples will be collected regardless of the time of last dose. The date and time of collection, will be recorded in the lab requisition form.

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 Bioanalysis 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 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 will also be included in the responder definition. The comparison is between the elagolix plus E2/NETA group and placebo group.

5.3.3.2 Secondary Variables

The key secondary measures of the Treatment Period that will be tested will include the following:

- Change from baseline in Overall Endometriosis-Associated Pain at Month 3, Month 6, and Month 12
- Change from baseline in DYS at Month 3, Month 6, and Month 12
- Change from baseline in NMPP at Month 3, Month 6, and Month 12
- Change from baseline in dyspareunia at Month 3, Month 6, and Month 12

- Change from baseline in PROMIS Fatigue Short Form 6a T-Score at Month 6 and 12

5.3.3.3 Additional Efficacy Variables

The following efficacy variables will be collected during the treatment period:

- Proportion of responders as assessed by change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, respectively.
- Proportion of responders as assessed by change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP and dyspareunia, respectively.
- Change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.
- Change from Baseline in analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary monthly.
- Proportion of analgesic use responders monthly (based only on reduction of rescue analgesics used).
- Monthly response in the PGIC and overall endometriosis-associated pain questionnaire.
- Change from baseline for each of six domains of EHP-30 questionnaire scores.
- Change from baseline for the EuroQoL-5D (EQ-5D-5L).
- Change from baseline for the WPAI:SHP.
- HCRU at each scheduled assessment.
- Change from baseline for the PROMIS Fatigue short Form 6A T-Score.

5.3.4 Safety Variables

- Bone mineral density and percentage change from baseline measured by DXA
- Summary of hypoestrogenic adverse events

- Proportion of subjects reporting adverse events
- Time to the first post-treatment menses
- Uterine bleeding measured by e-Diary
- Clinical laboratory parameters
- Vital signs and body weight
- Endometrial biopsy and TVU findings

5.3.5 Pharmacodynamic Variables

Concentrations of estradiol will be obtained throughout the Treatment Period. Additional pharmacodynamic parameters may be calculated if useful in the interpretation of the data.

5.3.6 Pharmacokinetic Variables

Exposures of elagolix and norethindrone will be summarized and elagolix concentrations may be used to develop a population pharmacokinetic model. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.7 Exploratory Research Variables

Exploratory Research Variables

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids, metabolites or hormone concentrations (estradiol). The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the study drug (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report.

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 study drug treatment and/or the 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, 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 would preclude the subject from continuing in the Treatment Period due to safety reasons
- The results of any post-baseline DXA prior to Month 48 document a Z-score (for subjects < 40 years of age) or T-score (for subjects ≥ 40 years of age) of < –2.5, a BMD decrease from baseline of > 8% in the lumbar spine, total hip or femoral neck, or due to TA MD assessment when the BMD percent change from baseline cannot be provided by the central reader
- 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
- 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.

- The subject requires surgical intervention for treatment of endometriosis or uterine bleeding (e.g., laparoscopy, hysterectomy, ovarian cystectomy)
- The Investigator and AbbVie TA MD deems it appropriate to protect the subject because the subject expresses suicidal ideation on the C-SSRS or via clinical interview at any time during the study.
- 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 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 Period 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 surgery (e.g., laparoscopy, hysterectomy, ovarian cystectomy) for the management of their 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 time point, a mammogram (only for subjects ≥ 40 years of age), DXA, TVU, Pap test, or endometrial biopsy does not need to be performed.

In addition, if a subject is being discontinued from the study due to a documented Z-score or T-score result of < –2.5, BMD decrease from baseline of > 8%, or TA MD assessment, 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 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

Subjects will be randomly assigned by IRT to receive one of the following treatment groups on randomization into the Treatment Period:

- elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD (n = 400)
- elagolix 200 mg BID (n = 100)
- placebo (n = 200)

The treatment administration for Treatment Period Day 1 through Month 6 is presented in Table 5.

Table 5. Treatments Administered (Day 1 – Month 6)

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

Treatment assignment will remain blinded through Treatment Month 12 for all subjects and subjects previously randomized to elagolix 200 mg BID alone will be re-assigned at Month 6 (in a blinded manner) to the elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD treatment group and continue with this dosing regimen throughout the remainder of the Treatment Period (Months 7 – 48).

The treatment administration for Treatment Months 7 through 12 is presented in Table 6.

Table 6. Treatments Administered (Month 7 – Month 12)

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

Study drug treatment after Treatment Month 12 will be open-label such that all subjects will receive elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD.

The treatment administration for Treatment Months 13 through 48 is presented in Table 7.

Table 7. Treatments Administered (Month 13 – Month 48)

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

The elagolix study drug, consisting of elagolix or matching placebo (Treatment Months 1 – 12 only), will be supplied in a carton. The E2/NETA study drug, consisting of E2/NETA or matching placebo, will be supplied in a separate carton. The subject will take the first elagolix/placebo dose (morning dose) and first E2/NETA/placebo dose of study drug at the study site on Day 1 (randomization). Subjects will be instructed to thereafter self-administer their study drug throughout the Treatment Period.

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 – 48, study drug kits will be dispensed at each on-site visit (Months 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, and 45), with enough to supply subjects until the next scheduled on-site visit. Study drug will be taken orally twice daily during the 48-month Treatment Period. A morning dose of 1 tablet (elagolix or placebo [Treatment Months 1 – 12 only]) and 1 capsule (E2/NETA or placebo) and an evening dose of 1 tablet (elagolix or placebo [Treatment Months 1 – 12 only]) 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 in order to promote compliance.

If the subject forgets to take the morning dose, she 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. The evening dose will be taken from the newly dispensed supply of study drug. Subjects must return all study drug containers at each monthly visit.

5.5.2 Identity of Investigational Products

Information about the drug formulations to be used in this study is presented in Table 8.

Table 8. Identity of Investigational Products

Study Drug	Formulation	Route of Administration	Trademark	Manufacturer
Elagolix (ABT-620)	200 mg film coated tablets	Oral	N/A	AbbVie
Matching Elagolix Placebo	Placebo tablets	Oral	N/A	AbbVie
E2/NETA*	Estradiol 1 mg/Norethindrone acetate 0.5 mg capsules*	Oral	N/A	Novo Nordisk, A/S Or Amneal Pharmaceuticals
Matching E2/NETA Placebo	Placebo capsules	Oral	N/A	AbbVie

* Commercially-available standard dose E2/NETA tablets are over-encapsulated.

5.5.2.1 Packaging and Labeling

AbbVie will supply blinded and open label study drug in monthly kits (i.e., cartons). Kits will consist of either:

- Elagolix or matching placebo, and
- E2/NETA capsules or matching placebo

Each kit contains 5 blister cards, with each blister card containing 7 days of study medication. There are 5 weekly blister cards in each kit (carton) to supply enough study drug for 4 weeks (28 days) of dosing, plus 1 week of additional study drug supply.

Each individual elagolix or matching placebo blister card contains 14 tablets for a 7-day (1 week) supply of study medication. Also, each E2/NETA or matching placebo blister card contains 7 capsules for a 7-day (1 week) supply of study medication.

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° 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

All subjects will be centrally randomized using an IRT. Before the study is initiated, contact information and user guidelines for IRT will be provided to each site. Study drug will be dispensed at the study visits outlined in Appendix C, Study Activities.

As subjects enter into either the Washout Period or the Screening Period, a unique subject number will be assigned to each subject by IRT. This unique subject number will be used for each subject throughout the study.

After confirming that the subject has met randomization criteria and prior to the Day 1 (randomization) dose, a unique randomization number will be provided via IRT.

Subjects will be randomly assigned by IRT to one of the treatment groups as outlined in Section 5.5.1 upon entry into the Treatment Period.

For the second 6 months of the Treatment Period (Months 7 – 12), subjects previously randomized to elagolix 200 mg BID alone will be re-assigned by IRT to the elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD treatment group as outlined in Section 5.5.1. At Treatment Month 12, all subjects will be re-assigned by IRT to receive open label elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD, including subjects previously randomized to placebo. Subjects re-assigned by IRT will not be assigned new subject numbers.

In the event a study drug kit becomes lost or damaged, the site can contact IRT to obtain an unscheduled study drug kit re-supply to dispense to the subject. Sites will register subjects as "Completed" or "Discontinued" (if the subject prematurely discontinues) at the end of the Treatment Period and will also indicate whether the subject will enter the Follow-Up Period.

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 randomized into treatment groups as described in Section 5.5.1.

Study drug will be administered at the study site on Day 1 (randomization). 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 AbbVie TA MD must be notified in order to assess 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 MD.

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 throughout the course of the study.

The IRT will provide access to blinded subject treatment information during 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 (e.g., antidote is available). 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 study visits throughout the Treatment Period, or Premature Discontinuation visit (if applicable). The study site personnel will assess 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 and evening each day.

Through month 12 of the Treatment Period which is blinded, daily recordings of study drug dosing will be obtained using a compliance packaging blister card for all subjects (for both elagolix/matching placebo and E2/NETA/matching placebo). Study site personnel will assess study drug compliance after review of the study drug blister cards returned by the subjects at on-site visits.

Through the Open Label Treatment Period, compliance packaging blister cards will not be used and blister cards without compliance packaging will be used instead. Study site personnel will assess study drug compliance after review of the study drug blister cards

returned by the subjects at on-site visits. The subject will be asked at each study visit (on-site and phone) to provide the dates and approximate times of the last 4 doses taken prior to the study visit which will be recorded in source and in the eCRF.

Sites will be provided scanning technology for direct access to the dosing and compliance data; sites are expected to scan all returned compliance packaging blister cards to obtain the dosing information at each of the on-site treatment Period visits when study drug is returned to the site by the subject. Any unused/unopened compliance packaging blister cards should be documented as such in the scanning technology source documentation. Sites are expected to use the compliance data to guide them in discussions with the subject regarding the importance of treatment compliance. Upon reviewing the dosing data, if the date(s) and time(s) for any of the last 4 doses of study drug (elagolix or E2/NETA or placebo) prior to the monthly Treatment Period visit or Premature Discontinuation visit are missing, the subject will be asked to confirm whether doses were taken and to provide the dates and approximate times of the last 4 doses prior to the study visit. In this case, the subject reported data will be recorded in source and in the eCRF. Sites will document when any blister cards are not returned or when compliance packaging blister cards cannot be scanned.

Sites should instruct subjects not to remove extra or multiple tablets/capsules from the blister cards all at once (e.g., transferring multiple doses into a separate pill organizer) and should only remove the study drug from the blister when it is the time to take the dose. If the compliance data shows incidence of removing a number of extra tablets/capsules, sites should re-train the subjects on the importance of only removing study medication when it is time to take the dose and record re-training in the source documents.

Discrepancies in the number of tablets/capsules dispensed minus the number of tablets/capsules to be taken versus the number of tablets/capsules returned will be clarified with the subject during the study visit. Appropriate information, including retraining if provided, should be recorded in the source documents.

It is at the discretion of the Investigator to discontinue subjects from the study who fail to take and/or return the appropriate amount of study drug.

Compliance packaging data and subject reported dosages will be used for exposure response analysis.

5.5.7 Drug Accountability

The study Investigator or designee will verify via direct recording in IRT 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.

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 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 Phase 3 study in premenopausal women 18 to 49 years of age with moderate to severe endometriosis-associated pain employs a randomized design during the Treatment Period, the first 12 months of which is double-blind, placebo-controlled. The remaining 36 months is open-label, active treatment. The randomized, double-blind, placebo-controlled study design is the standard for unbiased assessments of treatment group differences. The randomized double-blind study design will allow for an unbiased evaluation of safety and efficacy.

5.6.2 Appropriateness of Measurements

The co-primary efficacy endpoints for this trial will be based upon the mutually-exclusive validated scales for daily assessment of DYS and NMPP measured by the 4-point Endometriosis Daily Pain Impact Diary. Use of protocol allowed analgesic medication for endometriosis-associated pain will be included in the responder definition of the primary endpoints. Additional efficacy measures of DYS and NMPP, dyspareunia, uterine bleeding scale, the PGIC, and overall endometriosis-associated pain (NRS) are widely used in endometriosis as assessment tools. In addition to assessment of pain reduction, the effects of treatment of endometriosis 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 following therapy. Given the known relationship between estradiol levels and bone loss, serum E2 measurements will also be utilized to assess potential bone effects of elagolix.

Subjects will be counseled at every visit on the importance of pregnancy prevention and use of appropriate and effective methods of contraception throughout the study as outlined in Section 5.2.4.

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-related 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 loss. 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-associated pain, similar to the ongoing Phase 3 registration program.

The maximum elagolix dose administered in this study will not exceed a total daily dose of 400 mg.

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 6.1.6. 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 (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 a causality or deemed it not assessable, AbbVie will consider the event associated.

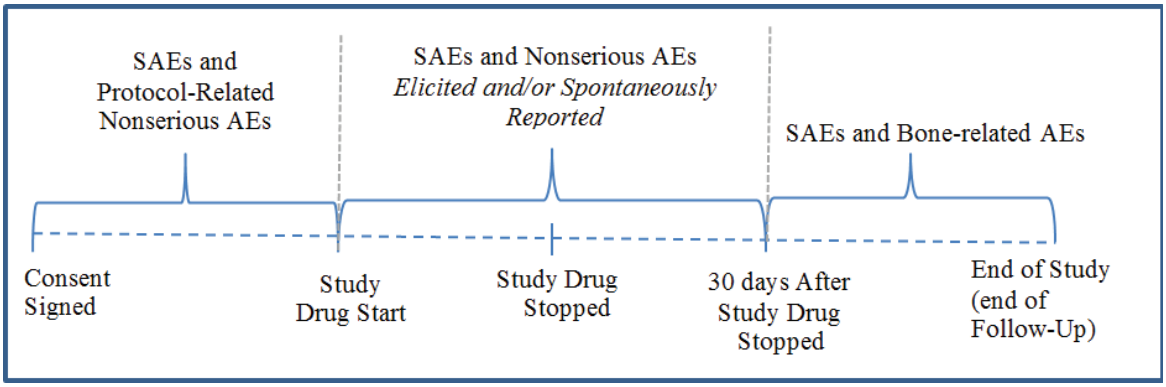
If an Investigator's opinion of "no reasonable possibility of being related to study drug" is given, an Other cause of event must be provided by the Investigator for serious adverse events.

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 administration 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:

General Medicine 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 physician listed below:

Primary Therapeutic Area Medical Director:

[redacted] MD, PhD
[redacted]
General Medicine, AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office: [redacted]
Mobile:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, 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]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with

global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours 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. 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. 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 the completion of the Follow-Up Month 1 study 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 has a positive serum pregnancy test during the Treatment or Follow-Up Periods of the study, no additional study procedures, including protocol required DXA scans, will be conducted. 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 Period 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:

[redacted], MD, PhD
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office:
Mobile:
Email:

Alternate Contact:

[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office:
Fax:
Email:

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 Analytical 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 safety and efficacy comparisons will be between the elagolix plus E2/NETA treatment group and the placebo group. Data from subjects randomized to elagolix 200 mg BID alone will be summarized separately from subjects randomized to the elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD arm. Unless otherwise specified, no statistical tests will be performed to evaluate potential differences between the two elagolix dose groups.

Data collected during the treatment period will be summarized by randomized treatment assignment on study Day 1.

- Subjects randomized to elagolix plus E2/NETA in the first 12 months of treatment.
- Subjects randomized to elagolix alone in the first 6 months of treatment
- Subjects randomized to placebo in the first 12 months of treatment

Analysis details will be specified in the statistical analysis plan. No statistical tests will be performed to evaluate potential differences between dose groups following the 12 month placebo-controlled portion of the 48-month Treatment Period.

8.1.2 Data Sets Analyzed

Full Analysis Set and Safety Analysis Sets

The full analysis set is comprised of all randomized subjects who took at least one dose of the study drug and subjects will be analyzed in the treatment group to which she was randomized. The full analysis set will be used for all efficacy and demographic analyses unless otherwise specified in the Statistical Analysis Plan (SAP). The safety analysis set is comprised of all randomized subjects who took at least one dose of study drug and subjects will be analyzed as the treatment actually received no matter what treatment group was assigned at the time of randomization. If a subject takes more than one treatment, the subject will be analyzed in the safety analysis set as taking the treatment to which she is randomized. All safety analyses will be performed based on safety analysis set.

8.1.3 Demographic, Baseline Characteristics and Concomitant Medications

Demographic and baseline characteristics will be summarized by treatment group.

Medical history will be summarized and presented using system organ classes (SOCs) and preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 or higher. The duration of the study drug exposure will be summarized by treatment group.

Protocol deviations and reasons for premature discontinuation will be summarized.

Concomitant medications will be coded using the World Health Organization (WHO) dictionary and summarized with frequencies and percentages.

Unless noted otherwise, the baseline values will be defined as the last value obtained prior to the initiation of elagolix, either in the first 12 months placebo controlled treatment period, (i.e., if the subject was randomized to active treatment on study Day 1) or

Months 13 – 48 of the treatment period (i.e., if the subject was randomized to placebo on study Day 1).

8.1.4 End of Placebo Controlled Treatment Period Analysis

An end-of-placebo-controlled treatment period analysis of the primary, secondary and other efficacy variables along with demographic and safety variables will be performed after the last subject completes the 12-Month placebo-controlled Treatment Period. These analyses will include data collected during the Treatment Period (placebo-controlled and open label) and Follow-Up Period. The database will be versioned for an interim lock and any discrepant data will be clarified before the versioning. Analyses will be performed by AbbVie.

Since this end-of-placebo-controlled treatment period analysis is the only and final analysis of the primary and key secondary endpoints, no additional adjustment of alpha-level is necessary.

8.1.5 Month 24 and Month 36 Analyses

At the end of Treatment Month 24 and Month 36, analysis of the efficacy and safety variables may be performed after the last subject completes the Treatment Month 24 and Month 36 visit, respectively. For subjects who prematurely discontinued during the treatment period, their data collected during the Follow-up Period will be included in the analysis, as appropriate. The database will be versioned for an interim lock and any discrepant data will be clarified before the versioning. Analyses will be performed by AbbVie.

8.1.6 Efficacy

Analysis details for the efficacy variables will be specified in the statistical analysis plan. Unless otherwise specified, no statistical tests will be performed following the 12 month placebo-controlled portion of the 48-month Treatment Period.

8.1.6.1 Primary Efficacy Variable

8.1.6.1.1 Primary Analysis

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

The co-primary efficacy endpoints will be the proportion of responders at Month 6 of the placebo-controlled Treatment Period 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. The elagolix plus E2/NETA dose group will need to demonstrate a statistically significantly greater proportion of responders for both co-primary endpoints (DYS and NMPP) in order for the elagolix plus E2/NETA dose group to be considered more efficacious than placebo for the co-primary endpoints.

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 pain as well as no increased analgesic rescue use for endometriosis-associated pain.

The specific drugs allowed for rescue analgesic use will be the following:

- NSAIDs (Naproxen 200 mg, ibuprofen 200 mg, diclofenac 25 mg, celecoxib 50 mg)
- opioid combination medication (5 mg Hydrocodone + 300 or 325 mg acetaminophen, 30 mg codeine + 300 mg acetaminophen)

The subjects will record use of these rescue analgesic medications on a daily basis in the e-Diary.

The definition of increased analgesic use is as follows:

- The average pill count of rescue analgesics within each class during the screening period will be summarized over the last 35 days prior to and including the first dose of study medication.

- For the primary endpoints of DYS and NMPP, subjects will be considered nonresponders if they have a 15% or greater increase in average pill count of rescue analgesics and analgesic change as further specified in Appendix I.

The rescue analgesic use for any defined period will be based on the average pill count for each class of rescue analgesics (endometriosis-associated): NSAID and opioids and any (NSAID 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 for the primary analysis, 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.

The pain threshold X will be determined at the end of the placebo-controlled treatment period prior to any unblinded analysis. The calculation of the threshold will be based on a receiver operating characteristics (ROC) analysis described below.

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 the 35 calendar days immediately prior to and including the Month 6 reference study day. 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), no change (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. All available subjects will be included in the ROC analysis. For subjects who prematurely discontinue before Month 6, the last available observation prior to discontinuation (Last Observation Carried Forward) will be used 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 threshold, will be included in the final Statistical Analysis Plan prior to blind break.

The primary analysis of the co-primary endpoint will be based on a logistic regression model including treatment as the main factor and baseline pain score as a covariate to compare the elagolix plus E2/NETA dose group to placebo. For subjects who prematurely discontinue before or at Month 6 of the placebo-controlled Period, last observation carried forward (LOCF) will be used in the primary responder analysis.

8.1.6.1.2 Sensitivity Analyses of the Primary Efficacy Variable

The following sensitivity analyses for each of the co-primary endpoints of the proportion of responders at Month 6 in pain scores will be conducted:

1. The difference between the elagolix plus E2/NETA and placebo in response rates will be analyzed using a chi-square test with a corresponding 95% CI for the difference in response rate based on normal approximation to the binomial distribution.
2. All subjects who prematurely discontinue the study drug at or before Month 6 will be considered as non-responders and the primary analysis will be repeated. Subjects who discontinue after Month 6 will be categorized as responders/non-responders in the same manner as done in the primary analysis.
3. The primary analysis will be repeated using mixed-imputation. In particular, subjects who discontinue prior to or at Month 6 due to an adverse event (AE) or lack of efficacy will be considered non-responders, while subjects who discontinue prior to or at Month 6 due to other reasons will have their monthly pain score carried forward following the LOCF rules previously described. Subjects who do not discontinue before Month 6 will be categorized as responders/non-responders in the same manner as done in the primary analysis.
4. All subjects who switched NSAIDs use at Baseline or Month 6 will be considered as non-responders and the primary analysis will be repeated.
5. All subjects who switched NSAIDs use at Baseline or Month 6 will be excluded from the primary analysis.
6. The following rules will be used to standardize different NSAIDs use and opioid use. The standardized rescue analgesic use will be re-evaluated based on Table 1 and the primary analysis will be repeated.
    - NSAID: 1 pill Naproxen = 1 pill Ibuprofen = 1 pill Diclofenac = 4 pills Celecoxib = 1 pill of NSAIDs use
    - Opioid: 1 pill hydrocodone + acetaminophen = 1 pills codeine phosphate + acetaminophen = 1 pill of opioid use

8.1.6.2 Secondary Efficacy Variables

A pre-specified multiple testing approach will be applied to maintain the family-wise type I error rate for the co-primary and key secondary endpoints. In order to test the key secondary endpoints, the null hypothesis for the co-primary endpoints for elagolix 200 BID plus E2/NETA versus placebo must be rejected. Subsequently, the key secondary endpoints may be tested following the multiple-testing procedure defined in the statistical analysis plan.

The key secondary measures of the Treatment Period that will be tested will include the following:

- Change from baseline in Overall Endometriosis-Associated Pain at Month 3, Month 6, and Month 12
- Change from baseline in DYS at Month 3, Month 6, and Month 12
- Change from baseline in NMPP at Month 3, Month 6, and Month 12
- Change from baseline in dyspareunia at Month 3, Month 6, and Month 12
- Change from baseline in PROMIS Fatigue Short Form 6a T-Score at Month 6 and 12

8.1.6.3 Other Efficacy Variables

Other efficacy endpoints during the treatment period will include the following (in no particular order).

- Proportion of responders as assessed by change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, respectively.
- Proportion of responders as assessed by change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP and dyspareunia, respectively.
- Change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.

- Change from Baseline in analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary monthly.
- Proportion of analgesic use responders monthly (based only on reduction of rescue analgesics used).
- Monthly response in the PGIC and overall endometriosis-associated pain questionnaire.
- Change from baseline for each of six domains of EHP-30 questionnaire scores.
- Change from baseline for the EuroQoL-5D (EQ-5D-5L).
- Change from baseline for the WPAI:SHP.
- HCRU at each scheduled assessment.
- Change from baseline for the PROMIS Fatigue short Form 6A T-Score.

The analyses for those other efficacy endpoints will be conducted at an alpha level of 0.05 without multiplicity adjustment. 95% CIs will be constructed as needed. Analysis details will be specified in the SAP.

Statistical Analyses for Secondary and Other Efficacy Variables

Generally, for continuous variables, including change from baseline analyses, treatment group differences will be analyzed as appropriate using analysis of covariance (ANCOVA) models with treatment group as the main effect and baseline score as a covariate. The mixed model with repeated measures (MMRM) method for change from baseline to each post-baseline assessment during the placebo controlled Treatment Period will be conducted as appropriate.

Categorical data will be analyzed using CMH test, chi-square, Fisher's exact test or logistic regression as appropriate.

During Months 13 – 48, visit values and change from baseline to each visit will be summarized by each group described in Section 8.1.1. No statistical tests of data from Months 13 – 48 will be performed.

Analysis details will be specified in the SAP.

8.1.6.3.1 Dysmenorrhea and Non-Menstrual Pelvic Pain

The mean change from baseline to each visit during the first 12 months of the placebo controlled treatment period in DYS and NMPP will be analyzed for each monthly visit. Monthly mean scores will be the average of the daily values reported during the 35 calendar days prior to and including the reference study day as defined in the SAP for the specific time point.

The proportion of responders in DYS and NMPP at Months 1 – 12 will be compared between the elagolix plus E2/NETA dosing group and the placebo group, based on the threshold for response determined for the primary analysis.

8.1.6.3.2 Dyspareunia

For dyspareunia, responses of "None," "Mild," "Moderate," and "Severe" will be assigned a score of 0, 1, 2, and 3, respectively. The dyspareunia monthly mean scores will be calculated as described above for DYS and NMPP. Responses of "Not applicable" will be excluded from the calculation. If a subject's mean score is not defined because all reports in that month are "Not applicable," then that mean score will be treated as a missing value and will not be included in analyses.

The proportion of responders at each post-baseline Months 1 – 12 visit will be compared between the elagolix plus E2/NETA dosing group and the placebo group. The threshold for defining responders will be determined using the same ROC method described for DYS and NMPP.

The mean change from baseline to each visit during the first 12 months of the Treatment Period in dyspareunia will be summarized similar to the method for DYS and NMPP. Monthly mean scores will be the average of the daily values reported during the 35 calendar days prior to and including the reference study day as defined in the SAP for the specific time point.

8.1.6.3.3 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 12 months of the Treatment Period.

The percentage of days a rescue analgesic for endometriosis-associated pain is taken by the subject will be calculated for the following analgesic categories: (a) NSAID or opioid endometriosis analgesics, and (b) opioid endometriosis analgesics. The percentage of days a subject takes an analgesic during each month will be calculated for each analgesic category using the 35 calendar day interval as noted previously.

The mean change from baseline to each visit during the first 12 months of the treatment period in percentage of days as well as monthly average dose of endometriosis analgesic use for each analgesic category will be compared between the elagolix plus E2/NETA dosing group and the placebo group. Baseline will be calculated as percentage of days of endometriosis analgesic use for each analgesic category during the last 35 calendar days prior to and including Day 1 during the Screening Period.

The average pill count for each class of rescue analgesic for each visit during the first 12 months of the placebo controlled treatment period will be calculated by adding the daily pill count of the corresponding class of rescue analgesic in the 35 calendar day period immediately prior to and including the day of the reference study day, except for Month 1, 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.

8.1.6.3.4 Patient Global Impression of Change (PGIC)

The number and percentage of subjects in each PGIC response category will be summarized monthly for the first 12 months of the placebo controlled treatment period for each treatment group and compared between the elagolix plus E2/NETA treatment group and the placebo group.

The percentage of subjects with response of "Much Improved" or "Very Much Improved" will be summarized.

8.1.6.3.5 Overall Endometriosis-Associated Pain Questionnaire

For the first 12 months of the placebo controlled treatment period, the mean change from baseline to each visit average NRS scores will be summarized for each treatment group and compared between the elagolix plus E2/NETA treatment group and the placebo group. The change in overall endometriosis-associated pain questionnaire NRS during Months 13 – 48 will be summarized.

8.1.6.4 Multiple Comparisons

The co-primary endpoint for the elagolix 200 BID plus E2/NETA group will be tested versus placebo and an $\alpha = 0.05$ level.

The key secondary endpoints will be tested following a pre-specified multiple testing procedure to control the Type I error rate and will be described in the Statistical Analysis Plan.

8.1.7 Safety

8.1.7.1 General Considerations

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

During the placebo-controlled treatment period (Months 1 – 12), baseline for all subjects will refer to the data obtained prior to Day 1. During the non-placebo controlled treatment period (Months 13 – 48), baselines will be defined as follows. For subjects randomized to elagolix or elagolix plus E2/NETA on Study Day 1, baseline for these subjects will refer to the baseline prior to the first dose of elagolix at the time of randomization. For subjects randomized to placebo in the first 12 months of the treatment period, their baseline will be reset to the data collected prior to reassignment at Month 13.

In general, for continuous variables, descriptive statistics (mean, standard deviation, median, minimum and maximum) will be summarized by treatment group. The treatment group differences in change and percent change from baseline will be analyzed using a one-way ANOVA with treatment as the main effect, or in some cases, one-way ANCOVA with treatment as the main effect, and baseline as a covariate. This will be detailed in the Statistical Analysis Plan.

Categorical data will be summarized with frequencies and percentages by treatment group. Fisher's exact test (or its generalization to r × c tables) will be used to analyze treatment group differences for qualitative categorical variables.

Unless specified otherwise, missing safety data will not be imputed.

Analysis details will be specified in the SAP.

8.1.7.2 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 for each treatment group. 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 AESI's (e.g., hypoestrogenic adverse events)

8.1.7.3 Analysis of Laboratory Data and Vital Signs

Changes from the baseline to each visit in continuous laboratory and vital sign parameters will be summarized by treatment group. Treatment group differences for changes from baseline during the first 12 months of the treatment period will be analyzed using a one-way ANOVA with treatment as the main effect.

Laboratory values will be categorized as low, normal or high based on normal ranges of the central laboratory used in this study. Low or high laboratory values will be flagged in the data listings.

The number of subjects reaching potentially clinically significant levels will be summarized by treatment group. Criteria will be summarized by treatment group.

8.1.7.4 Bone Mineral Density

The key BMD assessment comparisons are at the lumbar spine at Month 6 and Month 12. Secondary BMD endpoints include total hip and femoral neck. The elagolix 200 mg BID plus E2/NETA (1 mg/0.5 mg) QD dose will be compared to placebo at Months 6 and 12 and will be compared to Elagolix 200 BID alone at Month 6 based on percent change from baseline.

Percent change from baseline in BMD during Months 13 through 48, as well as Z-score and T-score values will also be summarized.

Full analysis details will be provided in the SAP.

Post-treatment bone mineral density scans will be summarized similarly, as appropriate. Percentage change from baseline in the post-treatment period will be compared with the percentage change from baseline at the end of the treatment period. There will be no statistical testing in the Follow-Up period.

Additional analysis details will be specified in the SAP.

8.1.7.5 Post-Treatment Analysis of Menstruation

The time of the first post-treatment menses onset relative to the date of the last dose of the study drug will be summarized.

8.1.7.6 Endometrial Biopsy

The number and percentage of subjects in each category of endometrial biopsy result will be summarized.

8.1.7.7 Transvaginal Ultrasound

Ultrasound assessments, listed below, will be summarized for each treatment group at each time point as appropriate.

- endometrial thickness
- uterine fibroids
- ovarian cysts

8.1.8 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.

8.2 Determination of Sample Size

Approximately 700 subjects will be randomized in a 4:1:2 ratio to elagolix 200 mg BID plus E2/NETA (N = 400), elagolix 200 mg BID alone (N = 100) or placebo (N = 200).

Assuming NMPP responder rates of 54% for the elagolix with E2/NETA therapy dose group and 35% for placebo, and DYS responder rates of 59% for the elagolix with E2/NETA therapy dose group and 23% for placebo, these sample sizes provide greater than 90% power to detect a difference in response rate between elagolix with E2/NETA and placebo, 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.

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.

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 washout (if applicable) or screening procedures being performed on the subject, the informed consent statement will be reviewed and 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.

An additional 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 consent to participate from the study, exploratory research 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 for their samples to be withdrawn. Once AbbVie receives the request, remaining exploratory research 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.

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 on the appropriate source documents. 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 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, the PGIC questionnaires and 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 overall endometriosis-associated pain questionnaire 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.

Source document verification will be performed. 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. 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, phone

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 Phase 3 Study to Evaluate the Safety and Efficacy of Elagolix in Combination with Estradiol/Norethindrone Acetate in Subjects with Moderate to Severe Endometriosis-Associated Pain
Protocol Date:	27 March 2020

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

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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 Development
		Clinical Development
		Clinical Pharmacokinetics
		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
Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase						X			
Hepatitis/HIV Screen		X							

Study Activities – Washout, Screening and Treatment Periods (Continued)

Activity	Washout[b]	Screening	Treatment Period[a]						
			Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Reflexive Thyroid Stimulating Hormone		X							
Urine Test for Gonorrhea and Chlamydia (optional)[n]		X							
Pharmacogenetic DNA/RNA blood sample (optional)			X						X
Pharmacogenetic endometrial sample (optional)		X							
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X			X
Pharmacodynamic Sample (E2)			X[o]	X	X	X	X	X	X
Begin E-Diary Daily Entry Endometriosis Daily Pain Impact Diary, Dyspareunia, Uterine Bleeding, Rescue Analgesic Use for Endometriosis-Associated Pain		X							
Endometriosis Health Profile-30 (EHP-30)			X			X			X
EuroQol-5D 5 level (EQ-5D-5L)			X			X			X
• PROMIS Fatigue Short Form 6a, • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)			X						X
IPAQ and Dietary Calcium Intake Questionnaire			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
Opioid Risk Tool (ORT)		X							

Study Activities – Washout, Screening and Treatment Periods (Continued)

Activity	Washout[b]	Screening	Treatment Period[a]						
			Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Health Care Resource Utilization (HCRU)			X	X	X	X	X	X	X
Overall endometriosis-associated pain via NRS[p]			X	X	X	X	X	X	X
PGIC				X	X	X	X	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			X						
Dispense Study Drug			X	X	X	X	X	X	X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 7	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**
Phone 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
Mammogram[i]						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)
Endometrial Biopsy[m]						X
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis						X
Vitamin D Testing						X
Subset of Chemistry Labs: ALT, AST, Alkaline Phosphatase		X				
Urine Test for Gonorrhea and Chlamydia (Optional)[n]						X
Pharmacogenetic DNA/RNA blood sample (optional)						X
Pharmacogenetic endometrial sample (optional)						X
Pharmacokinetic Sample (elagolix and norethindrone concentration)				X		X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Pharmacodynamic Sample (E2)		X		X		X
End E-Diary Daily Entry Endometriosis Daily Pain Impact Diary, Dyspareunia, Uterine Bleeding, Rescue Analgesic Use for Endometriosis-Associated Pain						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)						X
IPAQ and Dietary Calcium Intake Questionnaire						X
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit		X		X		X
Health Care Resource Utilization (HCRU)	X	X	X	X	X	X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X
PGIC		X		X		X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X
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
Phone 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)						X
IPAQ and Dietary Calcium Intake Questionnaire						X
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit			X			X
Health Care Resource Utilization (HCRU)	X	X	X	X	X	X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X
PGIC			X			X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 13	Month 14	Month 15	Month 16	Month 17	Month 18
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X
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
Phone Contact	X	X		X	X	
Physical Exam						X[h]
Gynecological (External Genitalia, Pelvic and Breast) Exam						X[h]
Vital Signs			X			X
TVU[j]						X
Mammogram[i]						X
DXA[l]						X
Pap smear						X
Pregnancy Tests:[j,k,l] urine (u) serum (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
Vitamin D testing						X
Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X			
Urine Test for Gonorrhea and Chlamydia (Optional)[n]						X
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X
Pharmacodynamic Sample (E2)			X			X
Health Care Resource Utilization (HCRU)	X	X	X	X	X	X
Smoking/Alcohol Assessment						X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 19	Month 20	Month 21	Month 22	Month 23	Month 24
• 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)						X
IPAQ and Dietary Calcium Intake Questionnaire						X
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit			X			X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X
PGIC			X			X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X
Birth Control Attestation			X			X
Dispense Study Drug			X			X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 25	**Month 26**	**Month 27**	**Month 28**	**Month 29**	**Month 30**
Phone 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)	X (u)	X (u)	X (u)
Lipids and Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X			X
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X
Pharmacodynamic Sample (E2)						X
• Endometriosis Health Profile-30 (EHP-30) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)						X
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit			X			X
Health Care Resource Utilization (HCRU)						X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X
Smoking/Alcohol Assessment						X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X
Birth Control Attestation			X			X
Dispense Study Drug			X			X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 31	Month 32	Month 33	Month 34	Month 35	Month 36
Phone Contact	X	X		X	X	
Physical Exam						X[h]
Gynecological (External Genitalia, Pelvic and Breast) Exam						X[h]
Vital Signs			X			X
TVU[j]						X
Mammogram[i]						X
DXA[l]						X
Pregnancy Tests:[j,k,l] urine (u) serum (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Endometrial Biopsy[m]						X
Lipids and Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X			
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis						X
Urine Test for Gonorrhea and Chlamydia (Optional)[n]						X
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X
Pharmacodynamic Sample (E2)						X
• Endometriosis Health Profile-30 (EHP-30) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)						X
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit			X			X
Smoking/Alcohol Assessment						X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]					
	Month 31	Month 32	Month 33	Month 34	Month 35	Month 36
Health Care Resource Utilization (HCRU)						X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X
Birth Control Attestation			X			X
Dispense Study Drug			X			X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period					
	Month 37	Month 38	Month 39	Month 40	Month 41	Month 42
Phone Contact	X	X		X	X	
Vital Signs			X			X
DXA[l]						X
Pregnancy Tests:[j,k,l] urine (u) serum (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Lipids and Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X			X
Urine Test for Gonorrhea and Chlamydia (Optional)[n]						X
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X
Pharmacodynamic Sample (E2)						X
Health Care Resource Utilization (HCRU)						X
• Endometriosis Health Profile-30 (EHP-30) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)						X
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit			X			X
Smoking/Alcohol Assessment						X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X
Birth Control Attestation			X			X
Dispense Study Drug			X			X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]						PD[q]
	Month 43	Month 44	Month 45	Month 46	Month 47	Month 48	
Phone 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[h]
Pap smear						X	X[q]
TVU[j]						X	X[q]
Mammogram[i]						X	X[q]
DXA						X	X[q]
Pregnancy Tests:[j,k,l] urine (u) serum (s)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Endmetrial Biopsy[m]						X	X[q]
Lipids and Subset of Chemistry Labs: ALT, AST & Alkaline Phosphatase			X				
Clinical/Safety Labs: Chemistry, Hematology, Lipid Panel & Urinalysis						X	X
Urine Test for Gonorrhea and Chlamydia (Optional)[n]						X	X
Pharmacokinetic Sample (elagolix and norethindrone concentration)						X	X
Pharmacodynamic Sample (E2)						X	X
Pharmacogenetic endometrial sample (optional)							X
• Endometriosis Health Profile-30 (EHP-30) • PROMIS Fatigue Short Form 6a • Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP)						X	X

Study Activities – Treatment Period (Continued)

Activity	Treatment Period[a]						PD[q]
	Month 43	Month 44	Month 45	Month 46	Month 47	Month 48	
Smoking/Alcohol Assessment						X	
Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit			X			X	
Health Care Resource Utilization (HCRU)						X	X
Overall endometriosis-associated pain via NRS[p]	X	X	X	X	X	X	X
Review Adverse Events & Analgesic Rescue/Concomitant Medication	X	X	X	X	X	X	X
Contraceptive Counseling/Contraceptive Dispensing (prn)	X	X	X	X	X	X	X[r]
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. Site will record the dates and approximate times of the last 4 doses of study drug taken prior to each on-site and phone study visit after Month 12 in source and in the eCRF.

b. Subjects using exclusionary hormonal or analgesic 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 should 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 ≥ 40 years of age at the time of entry into Screening, if no mammogram has been performed within 3 months. During the Treatment Period, mammograms will also be performed for subjects who are 40 years of age or older at the time of the scheduled study visit. A mammogram is not required at Premature Discontinuation if a study mammogram was performed within approximately 6 months prior to the PD visit. Mammograms will be read locally.

Study Activities – Treatment Period (Continued)

j. For any subject who has a positive serum pregnancy test result during the Treatment Period up through 30 days post last dose of study drug, 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, 25 – 26, 28 – 29, 31 – 32, 34 – 35, 37 – 38, 40 – 41, 43 – 44, and 46 – 47. 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 phone contact visits. A positive urine pregnancy test result must be confirmed with a serum pregnancy test.

m. A negative urine pregnancy result should be obtained on the day of endometrial biopsy, prior to performing the procedure. An endometrial biopsy is not required during the Treatment Period if the subject's concurrent TVU indicates an endometrial thickness < 4 mm. If the subject's concurrent TVU indicates an endometrial thickness ≥ 4 mm, a biopsy must be performed.

n. Optional 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. On Day 1, the Pharmacodynamic sample should be collected with the safety labs prior to dosing.

p. 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.

q. Premature Discontinuation prior to the time of the Treatment Month 6 visit or within six months of a mammogram, DXA, TVU, Pap test, or endometrial biopsy does not require a mammogram, DXA, TVU, Pap test, or endometrial biopsy.

r. 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		
Estradiol (E2) sample	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
Return to Menses Questionnaire[h]	X[i]		

a. The Follow-Up Period for the study will conclude for all subjects 30 days after the last Treatment Month 48 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. DXA scans in Follow-Up may be performed ± 15 days around the respective study visit.

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. 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, 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 findings
- 3 – Probably benign
- 4 – Suspicious abnormality
- 5 – Highly suspicious of malignancy
- 6 – Known biopsy with proven malignancy

Appendix E. Overall Endometriosis-Associated Pain Questionnaire

Within the past 7 days on a scale of 0 – 10, 0 being no pain and 10 being worst pain ever, how do you rate your endometriosis pain?

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. Dietary Calcium Intake Questionnaire

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)	1/2 cup	
Ice cream (vanilla)	½ cup	
Mozzarella cheese (part skim)	1 ½ ounces	
Cheddar cheese	1 ½ ounces	
Sour cream (reduced fat)	2 tablespoons	
Cottage cheese (1% milk fat)	1 cup	
Cream cheese (regular)	1 tablespoon	
Vegetables, Fruits, Nuts and Beans		
Turnip greens (fresh, boiled)	1/2 cup	
Broccoli (raw)	1/2 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)	1/2 cup	
Tofu (firm, made with calcium sulfate)	1/2 cup	

Food Type	Standard Serving Size	Number of Servings on Average
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	

Note: National Institutes of Health 2016.[15]

Appendix H. Return to Menses Questionnaire

Return To Menses Questionnaire Version 2.0-SAMPLE

1. Has the subject had a menstrual period since stopping study drug?

☐ Yes ☐ No*

If Yes, when did the subject's first menstrual period start? _____
mm/dd/yyyy

How many days did it last? _____

What is (or was) the intensity of the subject's menstrual period?

☐ Light

☐ Moderate

☐ Heavy

*** If subject responded 'No' to question 1 at the Follow-Up Month 1 visit, site staff will ask the same question at the Follow-Up Month 6 and/or Follow-Up Month 12 visit, as applicable. Site staff will also ask the subject to keep track of and record the start date of her menstrual period so that it can be reviewed and documented at the subsequent Follow-Up Period visit.**

Return to Menses Questionnaire-English-USA-v2; 06Apr2018

Appendix I. 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
	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.

Appendix J. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Methodology:
Heading "Screening Period:"
Ninth sentence previously read:

Protocol allowed analgesic rescue medication for endometriosis-associated pain will include multiple equivalent non-steroidal anti-inflammatory drug (NSAID) choices and 2 opioid choices: codeine plus acetaminophen or hydrocodone plus acetaminophen; use of other rescue analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed during this period.

Has been changed to read:

Protocol allowed analgesic rescue medication for endometriosis-associated pain will include multiple non-steroidal anti-inflammatory drug (NSAID) choices and 2 opioid choices: codeine plus acetaminophen or hydrocodone plus acetaminophen; use of other rescue analgesic or prophylactic analgesic medications for endometriosis-associated pain will not be allowed during this period.

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Efficacy:"
Subheading "Secondary Efficacy Variables:"
Add: new subheading title and text

Secondary Efficacy Variables:

- Change from baseline in Overall Endometriosis-Associated Pain at Month 3, Month 6, and Month 12
- Change from baseline in DYS at Month 3, Month 6, and Month 12
- Change from baseline in NMPP at Month 3, Month 6, and Month 12
- Change from baseline in dyspareunia at Month 3, Month 6, and Month 12
- Change from baseline in PROMIS Fatigue Short Form 6a T-Score at Month 6 and 12

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Efficacy:"
Subheading "Additional Efficacy Variables:"
Bullet list previously read:

- DYS
- NMPP
- Dyspareunia
- Overall endometriosis-associated pain
- Proportion of responders as assessed by change and percent change from Baseline in average pain score and analgesic use monthly for DYS, NMPP, and dyspareunia
- Proportion of responders as assessed by change and percent change from Baseline in the average pain score alone (i.e., not taking into consideration analgesics use) monthly for DYS, NMPP, and dyspareunia, respectively.
- Analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary
- Patient Global Impression of Change (PGIC) questionnaire
- Patient reported outcome (PRO) and Outcomes Rating Scales questionnaires including: Endometriosis Health Profile-30 (EHP-30), EuroQol-5D (EQ-5D-5L), Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI:SHP), Health Care Resource Utilization (HCRU) and PROMIS Fatigue short Form 6a

Has been changed to read:

- Proportion of responders as assessed by change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, respectively.
- Proportion of responders as assessed by change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP and dyspareunia, respectively.
- Change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.
- Change from Baseline in analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary monthly.
- Proportion of analgesic use responders monthly (based only on reduction of rescue analgesics used).
- Monthly response in the PGIC and overall endometriosis-associated pain questionnaire.
- Change from baseline for each of six domains of EHP-30 questionnaire scores.
- Change from baseline for the EuroQoL-5D (EQ-5D-5L).
- Change from baseline for the WPAI:SHP.
- HCRU at each scheduled assessment.
- Change from baseline for the PROMIS Fatigue short Form 6A T-Score.

Section 3.4 Benefits and Risks
Second sentence previously read:

Elagolix has been administered to over 3,700 subjects to date, and has been generally well tolerated.

Has been changed to read:

Elagolix has been administered to over 4,800 subjects to date, and has been generally well tolerated.

Section 5.1 Overall Study Design and Plan: Description
Subsection Screening Period
Third paragraph, sixth sentence previously read:

Subjects will be allowed to take protocol allowed analgesic rescue medication for endometriosis-associated pain which includes multiple equivalent NSAID choices and opioid choices.

Has been changed to read:

Subjects will be allowed to take protocol allowed analgesic rescue medication for endometriosis-associated pain which includes multiple NSAID choices and opioid choices.

Table 2. Prohibited Medications
Subsection Prohibited During the Washout, Screening and Treatment Periods and thru Follow-Up Month 1
"Hormonal Medications and Non-hormonal Estrogen Supplements, such as:"
Delete: "GnRH antagonists (other than elagolix)"

GnRH antagonists (other than elagolix)

Table 2. Prohibited Medications
Subsection Prohibited During the Screening, Treatment, and Follow-Up Periods
Add: "GnRH antagonists (including investigational ones), such as:"

Prohibited During the Screening, Treatment, and Follow-Up Periods	
GnRH antagonists (including investigational ones), such as:	Orilissa®, relugolix

Section 5.2.4 Contraception Recommendations and Pregnancy Testing
Subsection Contraception Counseling/Dispensing Contraceptives
Fifth paragraph, first sentence previously read:

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.

Has been changed to read:

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 study drug and has returned to menses.

Section 5.3.1.1 Study Procedures
Subsection Mammogram
Last paragraph
Add: new second sentence

Mammograms may be performed within approximately ± 15 days of the scheduled corresponding visit.

Section 5.3.1.1 Study Procedures
Subsection TVU
Fifth paragraph, first sentence previously read:

During the Treatment Period, a TVU will also be performed at Month 12, Month 24, Month 36, and Month 48 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).

Has been changed to read:

During the Treatment Period, a TVU will also be performed at Month 12, Month 24, Month 36, and Month 48 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 6 months prior to the PD visit).

Section 5.3.1.1 Study Procedures
Subsection Bone Mineral Density (DXA Scan)
Heading "DXA Scans Performed for Subjects who Prematurely Discontinue in the Treatment Period"
Last bullet previously read:

Subjects who discontinue any time at the time of or after the Treatment Month 6 visit.

Has been changed to read:

Subjects who discontinue any time at the time of or after the Treatment Month 6 visit, or if one was not performed within approximately 6 months of the PD visit.

Section 5.3.1.1 Study Procedures
Subsection Endometrial Biopsy
Last paragraph, first and second sentence previously read:

An endometrial biopsy is not required during the Treatment Period if the TVU findings at Treatment Month 12, 24, 36, or 48 indicate an endometrial thickness < 5 mm. If the TVU findings at any visit time point during the Treatment Period indicate an endometrial thickness ≥ 5 mm, then the subject must have an endometrial biopsy performed and the AbbVie TA MD must be notified to assess the subject's continued eligibility.

Has been changed to read:

An endometrial biopsy is not required during the Treatment Period if the TVU findings at Treatment Month 12, 24, 36, 48, or Premature Discontinuation indicate an endometrial thickness < 4 mm. An endometrial biopsy is also not required at Premature Discontinuation if one was performed within approximately six months of the subject discontinuing from the study. If the TVU findings at any visit time point during the Treatment Period indicate an endometrial thickness ≥ 4 mm, then the subject must have an endometrial biopsy performed and the AbbVie TA MD must be notified to assess the subject's continued eligibility.

Section 5.3.1.1 Study Procedures
Subsection Pap Test
Last paragraph
Add: new last sentence

A Pap Test is not required at PD if one was performed within approximately six months prior to the PD visit.

Section 5.3.1.1 Study Procedures
Subsection Patient Reported Outcomes (PRO) and Outcomes Rating Scales
Heading "Overall Endometriosis-Associated Pain"
Last sentence previously read:

Site staff will record the subject's response electronically via a tablet device.

Has been changed to read:

Site staff will record the subject's response electronically via a tablet device at the time of the visit.

Section 5.3.1.1 Study Procedures
Subsection Health Care Resource Utilization (HCRU)
Third sentence previously read:

At all Treatment Period study visits (on-site and phone 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.

Has been changed to read:

At subsequent Treatment Period study visits (on-site and phone 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 (Treatment Month 1 to Treatment Month 24) or in the last six months (Treatment Month 25 to Treatment Month 48).

Section 5.3.1.1 Study Procedures
Subsection Post-Treatment Assessment of Menstruation
First sentence previously read:

Subjects will be asked about return to menses using the Return to Menses Questionnaire (Appendix H) in the Follow-Up Period, as outlined in Appendix C.

Has been changed to read:

Subjects will be asked about post-treatment to menses using the Return to Menses Questionnaire (Appendix H) in the Follow-Up Period, as outlined in Appendix C.

Section 5.3.3.2 Secondary Variables
Add: new section title and text

5.3.3.2 Secondary Variables

The key secondary measures of the Treatment Period that will be tested will include the following:

- Change from baseline in Overall Endometriosis-Associated Pain at Month 3, Month 6, and Month 12
- Change from baseline in DYS at Month 3, Month 6, and Month 12
- Change from baseline in NMPP at Month 3, Month 6, and Month 12
- Change from baseline in dyspareunia at Month 3, Month 6, and Month 12
- Change from baseline in PROMIS Fatigue Short Form 6a T-Score at Month 6 and 12

Section 5.3.3.2 Additional Efficacy Variables
Bullet list previously read:

- DYS
- NMPP
- Dyspareunia
- Overall endometriosis-associated pain
- Proportion of responders as assessed by the change and percent change from Baseline in average pain score and analgesic use for DYS, NMPP, and dyspareunia
- Proportion of responders as assessed by change and percent change from Baseline in the average pain score alone (i.e., not taking into consideration analgesic use) for DYS, NMPP, and dyspareunia,
- Analgesic use (average pill counts) to treat endometriosis-associated pain, as assessed using information from e-Diary
- Patient Global Impression of Change (PGIC) questionnaire
- Patient reported outcome (PRO) and Outcomes Rating Scales questionnaires including: EHP-30, EuroQoL 5D (EQ-5D-5L), WPAI:SHP, HCRU, and PROMIS Fatigue short Form 6A

Has been changed to read:

- Proportion of responders as assessed by change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, respectively.

- Proportion of responders as assessed by change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP and dyspareunia, respectively.
- Change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.
- Change from Baseline in analgesic use (average pill counts) to treat endometriosis-related pain, as assessed using information from the e-Diary monthly.
- Proportion of analgesic use responders monthly (based only on reduction of rescue analgesics used).
- Monthly response in the PGIC and overall endometriosis-associated pain questionnaire.
- Change from baseline for each of six domains of EHP-30 questionnaire scores.
- Change from baseline for the EuroQoL-5D (EQ-5D-5L).
- Change from baseline for the WPAI:SHP.
- HCRU at each scheduled assessment.
- Change from baseline for the PROMIS Fatigue short Form 6A T-Score.

Section 6.1.5 Adverse Event Reporting
"Men's and Women's Health Safety Team" previously read:

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:
Fax:
Email: [redacted]

Has been changed to read:

General Medicine Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

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

Section 6.1.6 Pregnancy
First paragraph, first sentence previously read:

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy.

Has been changed to read:

Pregnancy in a study subject must be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy.

Section 8.1.4 End of Placebo Controlled Treatment Period Analysis
First paragraph, second and third sentence previously read:

These analyses will only include data collected during the 12-month, placebo-controlled period and will not include data collected during Months 13 through 48 of the Treatment Period (not placebo-controlled) or the Follow-Up Period. The database will be versioned for an interim soft lock and any discrepant data will be clarified before the versioning.

Has been changed to read:

These analyses will include data collected during the Treatment Period (placebo-controlled and open label) and Follow-Up Period. The database will be versioned for an interim lock and any discrepant data will be clarified before the versioning.

Section 8.1.5 End of Treatment Month 24 Analysis
Section title and text previously read:

8.1.5 End of Treatment Month 24 Analysis

An end of treatment Month 24 analysis of the efficacy and safety variables will be performed after the last subject completes the Treatment Month 24 Visit. These analyses will only include data collected during the Months 13 through 24 of the Treatment Period (first 12 months of open-label period), and will not include data collected during the 12-month placebo-controlled period. For subjects who premature discontinued during the first 24 months of treatment period, their data collected during the Follow-up Period will be included in the analysis, as appropriate. The database will be versioned for an interim soft lock and any discrepant data will be clarified before the versioning. Analyses will be performed by AbbVie.

Has been changed to read:

8.1.5 Month 24 and Month 36 Analyses

At the end of Treatment Month 24 and Month 36, analysis of the efficacy and safety variables may be performed after the last subject completes the Treatment Month 24 and Month 36 visit, respectively. For subjects who prematurely discontinued during the treatment period, their data collected during the Follow-up Period will be included in the analysis, as appropriate. The database will be versioned for an interim lock and any discrepant data will be clarified before the versioning. Analyses will be performed by AbbVie.

Section 8.1.6.1.1 Primary Analysis
Seventh paragraph, last sentence previously read:

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.

Has been changed to read:

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 for the primary analysis, 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.

Section 8.1.6.1.2 Sensitivity Analyses of the Primary Efficacy Variable
Item 1 previously read:

The difference between the elagolix plus E2/NETA and placebo in response rates will be analyzed using a chi-square test with a corresponding 97.5% CI for the difference in response rate based on normal approximation to the binomial distribution.

Has been changed to read:

The difference between the elagolix plus E2/NETA and placebo in response rates will be analyzed using a chi-square test with a corresponding 95% CI for the difference in response rate based on normal approximation to the binomial distribution.

Section 8.1.6.1.2 Sensitivity Analyses of the Primary Efficacy Variable
Add: new Item 4, 5 and 6

4. All subjects who switched NSAIDs use at Baseline or Month 6 will be considered as non-responders and the primary analysis will be repeated.
5. All subjects who switched NSAIDs use at Baseline or Month 6 will be excluded from the primary analysis.
6. The following rules will be used to standardize different NSAIDs use and opioid use. The standardized rescue analgesic use will be re-evaluated based on Table 1 and the primary analysis will be repeated.
    - NSAID: 1 pill Naproxen = 1 pill Ibuprofen = 1 pill Diclofenac = 4 pills Celecoxib = 1 pill of NSAIDs use

- Opioid: 1 pill hydrocodone + acetaminophen = 1 pills codeine phosphate + acetaminophen = 1 pill of opioid use

Section 8.1.6.1.2 Sensitivity Analyses of the Primary Efficacy Variable
Delete: last paragraph

The primary analysis and the sensitivity analyses specified above 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 monthly average pain score will be conducted in the same manner as for the change from baseline.

Section 8.1.6.2 Secondary Efficacy Variables
First bullet previously read:

Change from baseline in NRS at Month 3, Month 6, and Month 12

Has been changed to read:

Change from baseline in Overall Endometriosis-Associated Pain at Month 3, Month 6, and Month 12

Section 8.1.6.2 Secondary Efficacy Variables
Add: new last bullet

Change from baseline in PROMIS Fatigue Short Form 6a T-Score at Month 6 and 12

Section 8.1.6.3 Other Efficacy Variables
First paragraph previously read:

Other efficacy endpoints during the first 12 months of the treatment period will include the following (in no particular order).

Has been changed to read:

Other efficacy endpoints during the treatment period will include the following (in no particular order).

Section 8.1.6.3 Other Efficacy Variables
First, second, and third bullet previously read:

- Proportion of responders as assessed by change and percent change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, 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 and dyspareunia, respectively.
- Change and percent change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.

Has been changed to read:

- Proportion of responders as assessed by change from Baseline in average pain score and analgesic use monthly for DYS, NMPP and dyspareunia, respectively.
- Proportion of responders as assessed by change from Baseline in average pain score alone (i.e., not taking into consideration of analgesic use) monthly for DYS, NMPP and dyspareunia, respectively.
- Change from Baseline, in the monthly average pain score (DYS, NMPP, and dyspareunia), as assessed using information from the e-Diary.

Section 8.1.6.3 Other Efficacy Variables
Tenth and eleventh paragraph previously read:

- Monthly response for the HCRU.
- Change from baseline for the PROMIS Fatigue short Form 6A.

Has been changed to read:

- HCRU at each scheduled assessment.
- Change from baseline for the PROMIS Fatigue short Form 6A T-Score.

Section 8.1.6.3.3 Analgesic Use for Endometriosis-Associated Pain
Third paragraph
Delete: last sentence

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 four types of NSAIDs specified in Table 3 and will not be conducted separately by NSAID type.

Section 15.0 Reference List
Reference 6 previously read:

AbbVie. ABT-620 (Elagolix) Investigator's Brochure Edition 18. 11 October 2018.

Has been changed to read:

AbbVie. ABT-620 (Elagolix) Investigator's Brochure Edition 19. 09 October 2019.

Section 15.0 Reference List
Add: new Reference 16

Bandolier. The Oxford League Table of Analgesic Efficacy. 2007 [cited 2019 Oct 14]. Available from:
http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/lftab.html.

Appendix C. Study Activities
Subsection <u>Study Activities – Treatment Period</u>
"Month 25" through "Month 30"
Activity "Pharmacodynamic Sample (E2)"
Column "Month 27"
Delete: "X"

X

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
"Month 37" through "Month 42"
Activity "Endometriosis Health Profile-30 (EHP-30)"
Column "Month 42"
Add: "X"

X

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
"Month 43" through "Month 48"
Activity "Pharmacokinetic Sample (elagolix and n3.3orethindrone concentration)"
Previously read:

Pharmacokinetic Sample (elagolix and n3.3orethindrone concentration)

Has been changed to read:

Pharmacokinetic Sample (elagolix and norethindrone concentration)

Appendix C. Study Activities
Subsection Study Activities – Treatment Period
Table note "m." and "q." previously read:

m. A negative urine pregnancy result should be obtained on the day of endometrial biopsy, prior to performing the procedure. An endometrial biopsy is not required during the Treatment Period if the subject's concurrent TVU indicates an endometrial thickness < 5 mm. If the subject's concurrent TVU indicates an endometrial thickness ≥ 5 mm, a biopsy must be performed.

q. Premature Discontinuation prior to the time of the Treatment Month 6 does not require a mammogram, DXA, TVU, Pap test, or endometrial biopsy.

Has been changed to read:

m. A negative urine pregnancy result should be obtained on the day of endometrial biopsy, prior to performing the procedure. An endometrial biopsy is not required during the Treatment Period if the subject's concurrent TVU indicates an endometrial thickness < 4 mm. If the subject's concurrent TVU indicates an endometrial thickness ≥ 4 mm, a biopsy must be performed.

q. Premature Discontinuation prior to the time of the Treatment Month 6 visit or within six months of a mammogram, DXA, TVU, Pap test, or endometrial biopsy does not require a mammogram, DXA, TVU, Pap test, or endometrial biopsy.