1.0 Title Page

Clinical Study Protocol M16-283

A Phase 3b Study to Evaluate the Long-Term Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

Incorporating Administrative Changes 1 and 2 and Amendments 1, 2, 3, 4, 5, and 6

AbbVie Investigational Product:	Elagolix (ABT-620)
Date:	02 May 2022
Development Phase:	3b
Study Design:	Phase 3b, sequential, randomized, 12-month double-blind placebo-controlled, 36-month open-label, multi-center study designed to evaluate the long-term safety of elagolix with add back therapy in women with heavy menstrual bleeding associated with uterine fibroids in premenopausal women 18 to 50 years of age
Investigators:	Multicenter Trial: Investigator information is on file at AbbVie
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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	17 May 2017
Amendment 1	29 June 2017
Amendment 2	24 May 2018
Administrative Change 1	09 May 2019
Administrative Change 2	13 May 2020
Amendment 3	05 September 2019
Amendment 4	16 November 2020
Amendment 5	08 October 2021

The purpose of this amendment is to:

- Update Section 5.3.1.1, Study Procedures, Endometrial Biopsy and Appendix C, Study Activities.

  Rationale: *Based on FDA correspondence to elagolix-AB IND 115528 (April 21, 2022, FDA Advice/Information Request, Reference ID: 4971727), the endometrial biopsy at Month 36 was reinstated and the criteria revised so that the endometrial biopsy is required regardless of endometrial thickness.*
- Correct administrative and typographical errors throughout the document.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-283
Name of Study Drug: Elagolix (ABT-620)	**Phase of Development:** 3b
Name of Active Ingredient: Elagolix sodium	**Date of Protocol Synopsis:** 02 May 2022
Protocol Title: A Phase 3b Study to Evaluate the Long-Term Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women	
Objectives: The objectives of this study are 1) to assess the safety of elagolix 300 mg BID in combination with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) compared to placebo at 12-months in premenopausal woman with heavy menstrual bleeding associated with uterine fibroids, 2) to characterize the impact of elagolix 300 mg BID with E2/NETA on bone mineral density (BMD) in women with heavy menstrual bleeding associated with uterine fibroids after up to 48-months of treatment.	
Investigators: Multicenter	
Study Sites: Approximately 175 sites	
Study Population: Premenopausal female subjects (aged 18 to 50 years, inclusive) with uterine fibroids and HMB (> 80 mL blood loss per menstrual cycle).	
Number of Subjects to be Enrolled: Approximately 500	
Methodology: This Phase 3b, sequential, randomized, 12-month double-blind placebo-controlled, 36-month open-label, multi-center study is designed to evaluate the long term safety of elagolix with add back therapy in women with HMB associated with uterine fibroids. Approximately 500 subjects will be randomized in a 2:1 ratio to one of the following two treatment groups: 1. Elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) (n = 335) for 48-months 2. Placebo (n = 165) for 12-months, followed by elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) for 36-months Subjects randomized to elagolix 300 mg BID plus E2/NETA in the 12-month Treatment Period will receive the same treatment during the open label Treatment Period. Subject randomized to placebo in the 12-month Treatment Period will switch to elagolix 300 mg BID plus E2/NETA during the open label Treatment Period after completing the 12-month Treatment Period.	
Study Duration: The total duration for this study is up to 77 months. The study consists of 4 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 2.5 to 5 Months prior to first dose of study drug. • Treatment Period – up to 48-month treatment duration.	

Study Duration (Continued):

- Post-Treatment Follow-Up Period – up to 12-month duration following the last dose of the study drug. Subjects are expected to enter Post-Treatment Follow-Up after completing Treatment Month 48, or at any time a subject prematurely discontinues during the Treatment Period.

Washout Period:

Following informed consent, subjects, who have been taking exclusionary medications, must enter a Washout Period. Subjects must complete the Washout Period and then have at least 1 menses (refer to Table 2) after completion of washout, prior to entering the Screening Period. The duration of 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, a physical examination with vital signs, urine pregnancy testing; protocol-related adverse event review and documentation of current medications and a pelvic ultrasound (transabdominal [TAU] and transvaginal [TVU]) may be performed after obtaining informed consent and prior to a subject entering the Washout Period in order to establish the presence of a qualifying fibroid(s) or uterine volume to avoid an unnecessary and lengthy washout period. Subjects will also begin the use of dual non-hormonal contraception and receive counseling on the importance of consistent, appropriate and effective use of birth control and will have contraceptives dispensed as necessary.

Screening Period:

Following informed consent (if Washout was not required), subjects will enter into the approximately 2.5 to 5 Months Screening Period to establish eligibility based on inclusion and exclusion criteria, including the following assessments: a pelvic ultrasound (TAU and TVU); a saline infusion sonohysterography (SIS); an endometrial biopsy; a Pap test; a mammogram in subjects 39 years of age or older (at the time of randomization) if one was not performed within 3 months prior to Screening; a dual energy x-ray absorptiometry (DXA) scan (for BMD). During the Screening Period, subjects must demonstrate MBL of > 80 mL for each of two menses as measured by the Alkaline Hematin method which quantifies the amount of blood loss on sanitary products. Subjects will be dispensed sanitary product collection kits for 2 to 3 menstrual cycles and will be required to collect all sanitary products (with or without visible blood) on days with menstrual bleeding or spotting, and must return the products to the site within approximately 5 days after cessation of menses. Subjects are required to use dual non-hormonal contraception (as applicable), contraceptive counseling will be provided and contraceptives dispensed, as necessary.

Year 1 Treatment Period:

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

On Day 1 of the 12-month Treatment Period, subjects will be randomized to receive either placebo (n = 165), or elagolix 300 mg BID plus E2/NETA (n = 335). Study drug kits will be dispensed to subjects at each on-site visit. Subjects entering the 12-month Treatment Period will have on-site visits at Day 1, Months 3, 6, 9 and 12; phone visits will be made at Months 1, 2, 4, 5, 7, 8, 10 and 11.

A mammogram, pelvic ultrasound (TAU and TVU) and endometrial biopsy (based on TVU finding) will be performed in subjects at Month 12 or Premature Discontinuation Visit, if applicable; DXA scan will be performed at the Months 6, 12 and Premature Discontinuation Visit (if applicable); Vital signs assessments will be conducted at all on-site study visits, and a baseline ECG will be obtained.

Year 1 Treatment Period (Continued):

During Months 1 to 12, subjects will be asked to complete the following patient-reported outcome questionnaires: (UFS-QoL), Patient Global Impression of Change (PGIC based on menstrual bleeding (PGIC-MB), Site Staff will administer the and the C-SSRS – Since Last Visit questionnaire. The Investigator will complete the Physician Surgery Questionnaire (PSQ).

A urine pregnancy test will be performed at each visit throughout the Treatment Period. Home urine pregnancy test kits will be provided to subjects for use at home for the study visits when subjects are not required to come to the site. Subjects will self-administer the test and report the results to the site during the scheduled 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.

Blood samples for Clinical Safety Labs will be performed at on-site visits throughout the 12-month Treatment Period. Subjects will be counseled at each visit on appropriate and effective forms of dual non-hormonal contraceptives to promote pregnancy prevention.

Blood samples will be collected for assay of serum estradiol and to measure plasma concentrations of elagolix and norethindrone.

Adverse event and concomitant medication review will be conducted at all visits (on-site and phone visit) during the Treatment Period.

Year 2, 3 4 (Open-Label) Treatment Period:

Subject randomized to placebo in the 12-month Treatment Period will switch to elagolix 300 mg BID plus E2/NETA during the open label Treatment Period after completing the 12-month Treatment Period. For subjects entering the open-label Treatment Period, visits will occur either by phone or on-site from Months 13 through 48. The study drug will be dispensed every 3 months (during an on-site visit). Study drug will be taken orally twice daily for the entire open label Treatment Period. A morning dose of 1 tablet (elagolix) and 1 capsule (E2/NETA) and an evening dose of 1 tablet (elagolix) should be taken each day approximately 12 hours apart.

During the phone visits, site personnel will discuss adverse events, concomitant medications, if applicable, obtain the results of the subject's self-administered urine pregnancy test, will remind subjects of the importance of consistent use of appropriate and effective dual non-hormonal contraception. Subjects may begin taking hormonal contraceptive preparations only after completing the Treatment Period, being off study drug for at least 30 days and having a negative urine pregnancy test. On-site visits will occur every three months starting at Month 15.

The following study procedures will be performed (as applicable); a pelvic ultrasound (TAU and TVU), Pap test, mammogram, and an endometrial biopsy starting at Month 24 to Month 48 or Premature Discontinuation Visit. DXA scans will be obtained every 6 months starting at Month 18 or Premature Discontinuation Visit (if applicable).

Subjects will also be asked to complete patient-reported outcome questionnaires, throughout the 36-month open-label Treatment period; the UFS-QoL and Site Staff will administer the C-SSRS – Since Last Visit.

Year 2, 3 4 (Open-Label) Treatment Period (Continued):

A urine pregnancy test will be performed at each visit throughout the Treatment Period. Home urine pregnancy test kits will be provided to subjects for use at home for the study visits when subjects are not required to come to the site. Subjects will self-administer the test and report the results to the site during the scheduled 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. Subjects will be counseled at each visit on appropriate and effective forms of dual non-hormonal contraceptives to promote pregnancy prevention.

Subjects will continue to provide blood samples for Clinical Safety Labs, during the on-site visits.

Post-Treatment Follow-Up Period:

Subjects will enter the Post-Treatment 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 any time during the Treatment Period will enter the Post-Treatment Follow-Up Period. DXA scans of the lumbar spine, total hip, and femoral neck will be obtained at Post-Treatment Follow-Up Months 6 and/or 12.

Pregnancy testing, samples for FSH and E2, Return to Menses questionnaire completion will be performed at designated study visits. Adverse events and concomitant medication use will also be reviewed. Subjects may begin taking hormonal contraceptive preparations only after completing the open-label Treatment Period, being off study drug for 30 days, having a negative urine pregnancy test and returning to menses.

Central Laboratory and Central Imaging Vendors:

DXA, Ultrasound (TAU/TVU), SIS, MRI (if applicable), Endometrial biopsy, Pap test and safety clinical lab samples will be analyzed/evaluated using the central laboratories or vendors. Assays for biomarkers, pharmacokinetics, and pharmacogenetics will be analyzed at AbbVie and those for the Alkaline Hematin will be analyzed by the Alkaline Hematin Laboratory.

Analysis of Menstrual Blood Loss:

This study will utilize the Alkaline Hematin method for measuring MBL during the Screening Period.

Key Criteria for Inclusion/Exclusion:

Key Inclusion Criteria:

- Subject is a premenopausal female 18 to 50 years of age at the time of Screening.
- Subject has a diagnosis of uterine fibroids documented by a Pelvic Ultrasound (TAU, TVU) assessed by a central reader and verification that a uterine fibroid meets at least one of the following criteria:
  - Intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter).
  - Subserosal fibroid ≥ 4 cm (longest diameter).
  - Multiple fibroids with a total uterine volume of ≥ 200 cm^3 to ≤ 2,500 cm^3.
- Subject has HMB associated with uterine fibroids as evidenced by MBL > 80 mL during each of two screening menses as measured by the alkaline hematin method.
- Subject has a Screening FSH level of < 35 mIU/mL (35 IU/L).
- Subject has a negative urine and/or serum pregnancy test(s) during the Washout (if applicable) and/or Screening Periods, and has a negative urine pregnancy test just prior to first dose.

Key Criteria for Inclusion/Exclusion (Continued):

- Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Washout (if applicable), Screening and Treatment Periods. Acceptable methods of dual contraception include the following combinations:
  - Condom with spermicide (foam, gel or polymer film).
  - Diaphragm with spermicide (condom may or may not be used).
  - Cervical cap with spermicide (condom may or may not be used).

  Subject is not required to use dual contraception methods if:
  - Sexual partner(s) is 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.
  - Subject had a bilateral tubal occlusion or tubal ligation at least 4 months prior to Screening.
  - Subject is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above.
- Subject has an adequate endometrial biopsy performed during Screening, the results of which show no clinically significant endometrial pathology.

Key Exclusion Criteria:

- Subject has had menstrual cycles that are > 38 days in length for the past 3 consecutive months prior to Screening.
- Subject has screening pelvic ultrasound or SIS results that show a clinically significant gynecological disorder such as:
  - A persistent simple ovarian cyst > 5 cm in longest diameter (if the pelvic ultrasounds shows a simple ovarian cysts > 5 cm and ≤ 7 cm, an ultrasound of the ovaries may be repeated in approximately 4 - 6 weeks; however, the results must be evaluated prior to Day 1 and not meet exclusion).
  - A complex ovarian cyst > 3.5 cm in diameter (longest diameter).
  - An endometrioma > 3.5 cm in diameter (longest diameter).
  - Large endometrial polyp ≥ 1 cm.
  - Intracavitary/submucosal pedunculated fibroid.
- Subject ≥ 21 years of age at Screening (or age at which Pap smears are routinely performed according to local guidelines) has a Pap smear result that meets exclusionary criteria.
- Subject's hemoglobin level is < 7 g/dL (subjects with initial screening hemoglobin results < 7 g/dL can be prescribed iron supplements and have their hemoglobin levels retested prior to Day 1).

Key Criteria for Inclusion/Exclusion (Continued):

- Subject has a history of osteoporosis **or** other metabolic bone disease, including:
  - Screening DXA results of the lumbar spine (L1 – L4), femoral neck, or total hip BMD corresponding to 2.0 or more standard deviations below normal (T-score ≤ –2.0).
  - Intercurrent bone disease (e.g., osteomalacia, osteogenesis imperfecta, etc.).
  - Condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, spinal hardware or severe scoliosis).
  - History or presence of a condition that is associated with a decrease in BMD (e.g., uncontrolled hyperthyroidism, uncontrolled hyperparathyroidism, anorexia nervosa, etc.).
  - History of low-trauma bone fracture (e.g., fracture resulting from a fall from a standing height or lower).
  - Bilateral hip replacement.
  - Clinically significant hypocalcemia, hypo- or hyperphosphatemia
  - Treatment with medication (excluding calcium and Vitamin D) for osteoporosis, osteopenia, or other bone disease associated with a decrease in BMD.
- Subject has a history of major depression or post-traumatic stress disorder (PTSD) episode within 2 years of screening, OR a history of other major psychiatric disorder at any time (e.g., schizophrenia, bipolar disorder).
- 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, intranasal or intra-articular injectable (for occasional use) corticosteroids are allowed.

Investigational Products:	Elagolix sodium 300 mg tablets Estradiol 1.0 mg/norethindrone acetate 0.5 mg
Doses:	Elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) (n = 335) Placebo (n = 165), switch to elagolix 300 mg BID plus E2/NETA after completing the 12-month Treatment Period
Reference Therapy:	Placebo to match Elagolix; Placebo to match E2/NETA
Mode of Administration:	Oral

Duration of Treatment: Subjects will receive up to 48 months of treatment.

Duration of Post-Treatment Follow-Up: Subjects will receive up to 12 months of Post-Treatment Follow-Up

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

The objective of this study is to evaluate the long term safety of Elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD), and as such, no primary efficacy endpoint is defined.

Criteria for Evaluation (Continued):

Questionnaires and Quality of Life Assessments:

- Reason for Study Participation
- PSQ
- UFS-QoL Questionnaire
- PGIC-MB
- C-SSRS
- Return to Menses

Safety:

Safety evaluations include physical examination, vital signs, ECG, BMD changes, endometrial assessments (endometrial thickness and biopsy), pelvic ultrasound (TAU/TVU), clinical laboratory tests (including hematology, chemistry, urinalysis and lipid panel) and adverse events monitoring.

Statistical Methods:

In general, data will be summarized for the 12-month double-blind Treatment Period, the 36-month open-label Treatment Period, and the Post-Treatment Follow-Up Period separately.

In the 12-month double-blind placebo-controlled Treatment Period, data will be summarized by treatment group (the elagolix 300 mg BID plus E2/NETA group and the placebo group). Comparisons will be made between the elagolix 300 mg BID plus E2/NETA group and the placebo group in the 12-month double-blind Treatment Period.

In the Year 2 to 4 open-label Treatment Period, summaries will be provided for each of the following groups of subjects.

1. Subjects randomized to elagolix 300 mg BID plus E2/NETA in the 12-month double-blind Treatment Period and continued to receive elagolix 300 mg BID plus E2/NETA in the open-label Treatment Period;
2. Subjects randomized to placebo in the 12-month double-blind Treatment Period, and switched to elagolix 300 mg BID plus E2/NETA in the open-label Treatment Period.

No statistical tests will be made following the 12-month double-blind placebo-controlled Treatment Period.

Efficacy:

Efficacy Analysis:

The objective of this study is to evaluate the safety of elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD), and as such, no primary efficacy endpoint is defined.

Analyses Other Efficacy Variables:

The change from baseline for UFS-QoL will be summarized by treatment group. During the double blinded period, change from baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as the main effect and corresponding baseline value as a covariate.

For the PGIC-MB, the individual and combined response categories will be summarized during the double blinded period. Comparison will be made using a Miettinen–Nurminen (M-N) test.

Statistical Methods (Continued):

Safety:

All randomized subjects who took at least one dose of the study drug will be included in the safety analyses. The number and percentage of subjects having adverse events will be tabulated by primary SOC and MedDRA Preferred Term with a breakdown by treatment group. Hematology, lipid panel, vital signs, endometrial safety via TVU/TAU and endometrial biopsy, and pregnancy results will be summarized.

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 percentage change from baseline will generally be analyzed using a 1-way analysis of variance (ANOVA) with treatment as the main effect in the 12-month Treatment Period, unless otherwise specified.

Categorical data will be summarized with frequencies and percentages by treatment group. Chi-square test or Fisher's exact test will be used to analyze treatment group differences for qualitative categorical variables as appropriate in the 12-month Treatment Period, unless otherwise specified.

The within-group percent change from baseline to Months 6, 12, 18, 24, 30, 36, 42 and 48 in BMD will be summarized for each treatment group. The percent change from baseline to Month 6 and Month 12 in BMD will be compared between the elagolix 300 mg BID plus E2/NETA group and the placebo group.

Sample Size:

Based on clinical review, a sample size of 500 was selected to gather long term safety exposure data in approximately 50 subjects completing 48 months of study drug dosing, with approximately 30 subjects receiving 48 months of active drug elagolix 300 mg BID plus E2/NETA 1/0.5 mg QD.

Pharmacokinetic:

Plasma concentrations of elagolix and norethindrone will be listed for each subject by visit day and dose regimen. Pharmacokinetic data may be combined with data from other studies in women to develop a population pharmacokinetic model. Exposure-response analyses may be conducted as appropriate.

Biomarker:

Serum concentrations of estradiol (E2) will be listed for each subject by visit day and dose regimen.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ABV	AbbVie
AE	Adverse Event
AESI	Adverse Event of Special Interest
AH	Alkaline Hematin
BID	Twice daily (bis in die)
BI-RADS	Breast Imaging Reporting and Data System
BMD	Bone Mineral Density
CIN	Cervical Intraepithelial Neoplasia
COVID-19	Coronavirus Disease - 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CSSR	Clinical Safety System Receipt
CU-IUD	Copper IUD
CYP3A	Cytochrome P450 3A
DFP	Direct-from-patient
DTP	Direct-to-patient
DXA	Dual energy X-Ray Absorptiometry
E2	Estradiol
E2/NETA	Estradiol/Norethindrone acetate
ECG	12-Lead Electrocardiogram
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
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
HDL	High-density lipoprotein
Hgb	Hemoglobin
HIFU	High Intensity Focused Ultrasound
HIV	Human Immunodeficiency Virus

HIV Ab	Human Immunodeficiency Virus Antibody
HMB	Heavy Menstrual Bleeding
HPV	Human Papilloma Virus
HSIL	High-Grade Squamous Intraepithelial Lesion
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
LDL	Low-density Lipoprotein
LNG-IUS	Levonorgestrel Intrauterine System
LSIL	Low-grade squamous intraepithelial lesion
M-N	Miettinen–Nurminen
M	Month (visit)
MBL	Menstrual Blood Loss
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NBI	Neurocrine Biosciences Inc
NETA	Norethindrone acetate
Pap	Papanicolau
PCV	Product Collection Visit
PGIC-MB	Patient Global Impression of Change – Menstrual Bleeding
PSQ	Physician Surgery Questionnaire
QD	Once a day
RANKL	Receptor activator of nuclear factor-κB ligand
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGOT/ASAT	Serum glutamic-oxaloacetic transaminase/aspartate aminotransferase
SGPT/ALAT	Serum glutamic-pyruvic transaminase/alanine aminotransferase
SIS	Saline Infusion Sonohysterography
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
TAU	Transabdominal Ultrasound

TEAEs	Treatment-emergent adverse events
TSH	Thyroid Stimulating Hormone
TVU	Transvaginal Ultrasound
UFS-QoL	Uterine Fibroid Symptom Quality of Life Questionnaire

Pharmacokinetic and Statistical Abbreviations

ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
MMRM	Mixed-model with repeated measures
PD	Pharmacodynamic
PK	Pharmacokinetic
SAP	Statistical Analysis Plan

Definition of Terms

Washout Period (if applicable)	The minimum interval of time for washout of hormonal therapy or other prohibited medications (if applicable).
Screening Period	The approximately 2.5 to 5 month period prior to randomization on Day 1, when screening procedures are performed to establish eligibility. Subjects may either enter the Screening Period directly, if no washout is required, or enter after completing the Washout Period (if applicable).
Day 1 (Randomization) or Treatment Period Day 1	The day a subject takes her first dose of study drug. Day 1 will occur between the first and tenth day of the onset (first day with full menstrual flow) of menses.
Month	A month is defined as 28 days.
Product Collection Visits (PCVs)	Visits at which subjects return used sanitary products for assessment of alkaline hematin levels (during screening); visits should occur within approximately 5 days after the last sanitary product was collected during a bleeding and/or spotting episode.
Heavy Menstrual Bleeding	Menorrhagia or > 80 mL blood loss

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3.0 Introduction

3.1 Uterine Fibroids

Uterine fibroids (leiomyomata) are the most common benign tumors in women and occur in up to 80% of women of reproductive age.[1] The incidence increases with age and uterine fibroids are the most common reason for hysterectomy in the United States.[2] Uterine fibroids may develop in African-American women on average 10 years earlier than in white women.[3] The overall cost of symptomatic uterine fibroids exceeds $2 billion per year in the United States.[4]

The growth of uterine fibroids is highly dependent on both estrogen and progesterone.[5]

Although often asymptomatic, fibroids may cause symptoms severe enough to warrant therapy in 20% to 50% of women[3] and the most common symptom is heavy or prolonged menstrual bleeding. Other symptoms may include anemia, pelvic pressure and pelvic organ compression, back pain, and adverse reproductive outcomes. Heavy menstrual bleeding (HMB) (menorrhagia, defined as greater than 80 mL per menstrual cycle) is extremely inconvenient, can significantly impact quality of life and may lead to iron-deficiency anemia.

While there are numerous surgical options available to manage symptomatic uterine fibroids, at present there is no long-term medical treatment for symptomatic uterine fibroids.

The ideal medical treatment for symptomatic uterine fibroids, as an alternative to surgical interventions, should control HMB, improve non-bleeding symptoms and quality of life, and prove safe and tolerable as a chronic therapy. Unfortunately, currently available medical options provide only short-term improvement of symptoms, and as such, are only indicated prior to surgery, and/or their side-effects limit their long-term use. A safe and effective chronic medical therapy for the management of HMB associated with uterine fibroids, as an alternative to hysterectomy or other surgical intervention, has not yet been approved.

3.2 Elagolix

Elagolix sodium (hereinafter "elagolix," also referred to as ABT-620) is a novel, oral, short-acting, non-peptide, gonadotropin-releasing hormone (GnRH) antagonist that competitively inhibits the GnRH receptors in the pituitary gland and is being developed by AbbVie for the management of endometriosis-related pain and the chronic management of heavy menstrual bleeding (HMB) associated with symptomatic uterine fibroids. The initial preclinical and clinical evaluation of elagolix was conducted by Neurocrine Biosciences Inc. (NBI). Safety results from these studies show that elagolix is generally well tolerated. Elagolix, unlike injectable GnRH analogs, produces a dose dependent suppression of pituitary and ovarian hormone levels in women, i.e., from partial ovarian suppression at lower doses to nearly full suppression at higher doses. A detailed discussion of the preclinical toxicology, metabolism, pharmacology and pharmacokinetics of elagolix in humans and a summary of clinical studies can be found in the Investigator's Brochure.[6]

3.2.1 Preclinical Experience

3.2.1.1 Toxicology

Please refer to the most recent edition of the elagolix Investigator Brochure for complete information on toxicology studies for elagolix.

3.2.2 Clinical Experience

Refer to the most recent version of the Investigator's Brochure for the complete information on clinical studies, exposure to study drug, and safety.

Clinical Program Overview

As of 20 August 2018, a total of 4,569 subjects have received at least 1 dose of elagolix in clinical studies conducted by NBI and AbbVie (39 Phase 1 studies, 6 Phase 2 endometriosis studies, 2 Phase 2 uterine fibroid studies [Studies M12-663 and M12-813], 2 Phase 3 endometriosis studies [Studies M12-665 and M12-671], 2 Phase 3

endometriosis extension studies [Studies M12-667 and M12-821]), and ongoing Phase 3 endometriosis studies [Study M14-702 and Study M16-383].

In women with HMB associated with uterine fibroids, 2 Phase 2 studies have been completed by AbbVie, Study M12-663 and Study M12-813. The Phase 3 uterine fibroid registration program consists of 2 pivotal studies, Study M12-815 and Study M12-817, and a single planned associated 6-month safety/efficacy extension study, Study M12-816. The Phase 3 uterine fibroid registration program has 790 subjects.

Clinical Pharmacokinetic and Pharmacodynamic Summary

See Investigator Brochure Section for detailed discussion regarding the pharmacodynamics of elagolix including results of the multiple-ascending dose study, Study M12-790, in premenopausal healthy female subjects.

As discussed in the Investigator Brochure, treatment of women with elagolix does not block ovulation so women may become pregnant while taking elagolix. There is a dose-dependent inhibition of ovulation with increasing elagolix dosing such that, for example, the 300 mg BID dose appeared to have a slightly lower ovulation rate than 200 mg BID (27% versus 32%), and when the standard-dose estradiol 1.0 mg/norethindrone acetate 0.5 mg (standard-dose E2/NETA) was co-administered with elagolix 300 mg BID, the formulation for the current study, the ovulation rate decreased further to approximately 10%.

Efficacy in Phase 2 Uterine Fibroid Studies

Please see the most recent version of Investigator Brochure for detailed description of the elagolix Phase 2b (Study M12-813) protocol and results. Results from Study M12-813 show that all treatment arms (both doses of elagolix [300 mg BID and 600 mg QD] alone or in combination with both strengths of E2/NETA in the form of Activella) met the primary endpoint, which was the proportion of subjects who achieved a Menstrual Blood Loss (MBL) volume of < 80 mL at the Final Month **and** 50% or greater reduction in MBL

volume from Baseline to the Final Month compared to that of placebo (all $P < 0.001$), as measured by the alkaline hematin method.

Additional results from Cohort 1 demonstrated that treatment with elagolix 300 mg BID plus E2/NETA showed the following:

- Clinically meaningful improvement in quality of life measures and symptom severity scores as assessed by UFS-QOL
- Mitigation of BMD loss at the lumbar spine, with standard-dose E2/NETA
- Substantial dose-dependent reduction in the incidence of vasomotor symptoms, e.g., hot flushes
- No evidence of endometrial safety concerns
- Overall safety profile remains unchanged, with no new or unexpected findings to date.

The conclusion from the Phase 2b study suggest that standard-dose E2/NETA as add-back therapy may be effective in preventing BMD loss during treatment with elagolix 300 mg BID, with minimal impact on primary efficacy bleeding endpoints in premenopausal women with HMB associated with uterine fibroids. This dosing regimen could potentially meet the objective of a long-term therapy for the management of symptomatic uterine fibroids in premenopausal women.

Adverse Events in Elagolix Uterine Fibroid Studies

Please see Investigator Brochure Section 8.3.3.1.5 for details of adverse events after elagolix treatment across the elagolix clinical program. This section will summarize the adverse event data in the elagolix Uterine Fibroid Phase 2b study.

Data from the completed Phase 2b study, Study M12-813, represent the most extensive single study data set that examined the tolerability of elagolix at dosing to be used in Phase 3, including the present study and show that, overall, the percentage of subjects who reported treatment-emergent adverse events was generally similar across all

treatment groups in both cohorts, ranging from 67.9% to 87.0%, with the highest values in the elagolix alone groups (300 mg BID, 80.0%; 600 mg QD, 87.0%). Estrogen-dependent adverse events from elagolix treatment were ameliorated significantly with the estrogen-progestin add-back regimens as detailed below.

The most common adverse events in both cohorts were hot flush, insomnia, and headache. The rates for hot flush in Cohort 1 were 3.1% for placebo and 44.6% for elagolix 300 mg BID alone, and the addition of low-dose or standard-dose E2/NETA significantly decreased the rates by approximately 20% and 34%, respectively (25.0% for elagolix 300 mg BID + low-dose E2/NETA and 10.8% for elagolix 300 mg BID + standard-dose E2/NETA). In Cohort 2, the rates of hot flush were 5.1% for placebo and 49.4% for elagolix 600 mg QD alone. Addition of low-dose or standard-dose E2/NETA significantly decreased the rates by approximately 31% and 35%, respectively (18.4% for elagolix 600 mg QD + low-dose E2/NETA and 14.3% for elagolix 600 mg QD + standard-dose E2/NETA).

Adverse events of special interest in elagolix clinical studies are discussed in the Investigator Brochure and include hot flush, cutaneous adverse events, ovarian-related events, BMD decrease, fractures, uterine bleeding, mood changing disorders (suicidality and depression) and changes in serum lipids.

In the completed Phase 2 studies in uterine fibroids, there were a higher percentage of women experiencing cutaneous/hypersensitivity events and hot flush with elagolix treatment compared with placebo. Adverse events of special interest will continue to be monitored in all clinical studies including the present study.

Serious Adverse Events in the Elagolix Uterine Fibroid Program

Please see Investigator Brochure Section 9.2.3.1.1 for details regarding Serious Adverse Events seen across the elagolix clinical program. This section will summarize the SAEs noted in the elagolix Phase 2b study, Study M12-813.

In Cohort 1 of the Phase 2b study in women with HMB associated with uterine fibroids, there were 13 serious adverse events (SAEs) that either occurred during the Treatment Period or within 30 days of last dose in 8 subjects randomized to receive active treatment. There were six SAEs in placebo treated subjects (9.2%), 3 (4.6%) in the elagolix 300 mg BID group, 3 (4.7%) in the elagolix 300 mg BID + LD E2/NETA group, and 1 (1.5%) in the elagolix 300 mg BID + SD E2/NETA group. Treatment-emergent SAEs were reported for 13 subjects in Cohort 2, including 1 subject (1.3%) in the placebo group, 5 (6.5%) in the elagolix 600 mg QD group, 3 (3.9%) in the elagolix 600 mg QD + LD E2/NETA group, and 4 (5.2%) in the elagolix 600 mg QD + SD E2/NETA group. In both cohorts, the majority of SAEs were reported by 1 subject each in any treatment group.

One subject in the elagolix 600 mg QD + LD E2/NETA group had an SAE of uterine leiomyoma that was considered reasonably possibly related to study drug.

Effects of Elagolix on Bone Mineral Density (BMD) in the Uterine Fibroid Phase 2b Study

In the 6-month Phase 2b study BMD was assessed at the lumbar spine (L1 – L4), femoral neck, and total hip via DXA at Screening and at Month 6 of the Treatment Period, or Premature Discontinuation.

Results from the Phase 2b uterine fibroid study demonstrate that treatment with elagolix 300 mg BID and 600 mg QD significantly decrease BMD, which is partially mitigated by addition of E2/NETA in a dose-dependent manner. In Cohort 1, the mean percentage change from Baseline to Month 6 in BMD in the lumbar spine for the elagolix 300 mg BID alone group was –3.8% at Month 6; 19% of subjects had a 3 to ≤ 5% BMD decrease, 29% had > 5% to < 8% BMD decrease, and 8% had a ≥ 8% BMD decrease.

In Cohort 2, the mean percentage change from Baseline to Month 6 in BMD in the lumbar spine for the elagolix 300 mg BID alone group was –3.4% at Month 6; 25% of subjects had a 3 to ≤ 5% BMD decrease, 21% had > 5% to < 8% BMD decrease, and 7% had a ≥ 8% BMD decrease. The addition of standard-dose E2 (estradiol 1.0 mg/norethindrone

acetate 0.5 mg) substantially mitigated BMD loss at the lumbar spine at Month 6 compared with the elagolix alone group. In Cohort 1 the mean change from baseline –0.1% versus –3.8%), while in Cohort 2 standard dose E2/NETA resulted in a mean change from baseline was –1.1% vs –3.4%.

After 6 months treatment in Cohort 1 in the standard E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) group 6.3% of subjects had a 3 to ≤ 5% BMD decrease, 1 subject (2%) had a 5% – 8% BMD decrease and no subjects had ≥ 8% BMD decrease at the lumbar spine. Similarly after 6 months treatment in Cohort 2 in the standard E2/NETA group 9.6% of subjects had a 3 to ≤ 5% BMD decrease, 3 subjects (5.8%) had a 5% – 8% BMD decrease and 1 subject (1.9%) had ≥ 8% BMD decrease at the lumbar spine.

Taken together results from the Study M12-813 indicated that the standard E2/NETA dose would ameliorate bone loss observed during treatment of heavy menstrual bleeding in women with uterine fibroids using elagolix 300 mg BID.

Effects of Elagolix on Clinical Laboratory Parameters

In the Phase 2 studies, changes in serum lipids, in particular total cholesterol and low-density lipoprotein cholesterol (LDL-C), were observed in this study, similar to those in which occur as women enter menopause[7] and these changes, as expected, were somewhat attenuated by E2/NETA in a dose-dependent manner. Mean percentage increases from Baseline in total cholesterol, high density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides were observed across each of the elagolix treatment groups over the 6-month treatment duration. Generally these mean changes were changes within the normal range of these laboratory tests. In all these studies, the increased lipid values usually occur during the first 1 to 2 months of elagolix use, stabilize or plateau, and return to pretreatment baseline levels within 1 to 3 months after elagolix is discontinued. Please see the latest version of the Investigator Brochure for details.

Uterine Bleeding in Phase 2 Studies in Uterine Fibroids

Studies with elagolix have shown that overall patients on elagolix experienced fewer days of bleeding per month, reduced bleeding intensity, and extended intervals between bleeding episodes compared with patients on placebo. Some subjects experienced periods of oligomenorrhea or amenorrhea with evidence of irregular bleeding as well, in particular at lower doses. The effect of elagolix on bleeding appeared to be dose-dependent.

Data from Phase 2b uterine fibroid study demonstrates that subjects reported no bleeding during the last 90 days on treatment most frequently in the elagolix 300 mg BID alone group and the elagolix 600 mg QD alone group, while the reports of no bleeding declined in a dose-dependent fashion with the addition of E2/NETA.

Of subjects who received elagolix and were amenorrheic upon entering the Post-treatment Follow-up Period, the majority of subjects (52% in Cohort 1 and 59% in Cohort 2) returned to menses at Month 1, and an additional 42% in Cohort 1 and 38% in Cohort 2 returned to menses at Month 2.

Endometrial Safety in Phase 2 Studies in Uterine Fibroids

Endometrial biopsies were conducted at Baseline and at Month 6 in Study M12-813. Results from Cohort 1 show that, among subjects in elagolix treatment groups, 39% to 43% had normal quiescent/minimally stimulated endometrium and 14% to 28% had normal proliferative endometrium at Month 6. No clinically significant findings were observed.

Results from Cohort 2 are similar. Among subjects in elagolix treatment groups, 21% to 36% had normal quiescent/minimally stimulated endometrium and 20% to 32% had normal proliferative endometrium at Month 6. No clinically significant findings were observed.

As would be expected from a molecule that decreases serum estradiol, there was no endometrial hyperplasia in women treated with elagolix alone in the Phase 2b uterine fibroid study nor was this observed after 6 months treatment with either addback arms.

3.2.3 Pregnancy in Elagolix Studies

Please refer to Section 8.3.3.10 of the most recent edition of the elagolix Investigator Brochure of a complete discussion of Pregnancies in the Elagolix Clinical Development Program. As discussed above and in the Investigator Brochure, elagolix does not block ovulation although there is a dose dependent inhibition of ovulation with increasing dosage.

Pregnancies have been observed in the elagolix clinical studies. Although there were no congenital malformations observed in the elagolix Phase 3 endometriosis program, earlier Phase 2 studies with elagolix did reveal 2 pregnancies with congenital malformations.

In the aforementioned Phase 2b UF (Study M12-813) study, 1 on-treatment pregnancy was reported. In the elagolix Phase 3 studies 4 on-treatment pregnancies were observed.

Extensive counseling on pregnancy prevention along with a requirement for dual non-hormonal barrier contraception is utilized in all ongoing and planned elagolix clinical trials. Pregnancies must be reported immediately and study drug discontinued. Information on the outcome of the pregnancy will be collected. For live infant births, information on the health of the infant will be collected 6 to 12 months after delivery.

Pregnancy outcomes must also be monitored vigilantly across the entire development program, including adverse events related to pregnancy outcomes. Women should also be counseled on the unknown, thus potential, risk to children born to mothers exposed to elagolix during pregnancy, including the possibility of malformations.

Phase 3 Clinical Development Program for Uterine Fibroids

The overall objective of the Phase 3 registration clinical development program is to generate requisite safety, tolerability, and efficacy data in 2 replicate 6-month Phase 3 pivotal studies and 1 safety and efficacy extension study (total 12-month treatment period) to support use of elagolix 300 mg BID with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) for the intended indication of the chronic management of HMB associated with uterine fibroids.

The primary objective of this current Phase 3b (Study M16-283) study in women with HMB associated with uterine fibroids is to obtain extended data on the safety of elagolix 300 mg BID with standard dose E2/NETA. All subjects will have the opportunity to be treated with elagolix 300 mg BID with standard dose E2/NETA for the second, third and fourth years of the study enabling a careful examination of the long term safety of this dose over 48 months, particularly with respect to bone loss compared to baseline.

3.3 Estradiol/Norethindrone Acetate

E2/NETA (1.0 mg E2 and 0.5 mg NETA) is a continuous combined oral estrogen/progestin regimen. E2/NETA is approved in the United States as postmenopausal hormone replacement therapy for the treatment of moderate to severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis. E2/NETA is also approved in the United States for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. The Phase 2b Study M12-813 demonstrated that elagolix 300 mg BID with full dose add-back therapy showed continued robust efficacy while mitigating bone loss in most study subjects. For this reason estradiol 1.0 mg/norethindrone acetate 0.5 mg is the only add-back therapy in this long-term treatment study.

3.4 Differences Statement

Phase 2 studies in women with HMB associated with uterine fibroids demonstrated that elagolix 300 mg BID provides the most robust efficacy in reducing HMB and E2/NETA

is the optimal regimen for managing and limiting BMD loss, such that longer term dosing is feasible.

Continued assessments of this treatment regimen in the pivotal Phase 3 trials will provide the requisite data to support registration of elagolix 300 mg BID + E2/NETA as safe and efficacious treatment for the chronic management of HMB associated with uterine fibroids.

This long-term study will demonstrate safety data of elagolix 300 mg BID plus estradiol 1.0 mg/norethindrone acetate 0.5 mg versus placebo over a 12-month period and the long term safety of this dose over 48 months, particularly with respect to bone mineral density.

3.5 Benefits and Risks

The most common symptom of premenopausal women with uterine fibroids is heavy menstrual bleeding (HMB). A safe and effective chronic pharmacologic therapy for symptomatic uterine fibroids, as an alternative to hysterectomy or other surgical intervention, has not yet been approved, which is the objective of the elagolix Phase 3 clinical development program. Results from Phase 2 studies in women with HMB associated with uterine fibroids demonstrated that treatment with elagolix 300 mg BID alone and in combination with E2/NETA provided robust efficacy in reducing HMB associated with uterine fibroids. Importantly, when co-administered with elagolix 300 mg BID, E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) mitigated BMD loss observed with elagolix 300 mg BID alone and substantially reduced other hypoestrogenic adverse events such as hot flushes. Also co-administration of elagolix and E2/NETA attenuated increases in serum lipid parameters observed with elagolix 300 mg BID alone. Furthermore, there was no evidence of endometrial safety concerns and the overall safety profile remained unchanged, with no new or unexpected findings to date.

This therapeutic approach, if successful, could provide an alternative to surgical interventions as a chronic pharmacologic treatment for heavy menstrual period associated with uterine fibroids. Based on the totality of data to date from the Phase 2 clinical

development program, the overall benefit/risk profile of elagolix 300 mg BID with E2/NETA appears to be favorable for the chronic management of HMB associated with uterine fibroids, and will be established in the Phase 3 pivotal trials. This Phase 3b study will extend understanding of the safety of elagolix 300 mg BID with E2/NETA compared to placebo for 12 months and the long term tolerability of this dose over 48 months, particularly with respect to bone mineral density compared to baseline.

Considering the coronavirus disease - 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Based on the information to date, no additional risk to study participants is anticipated with the use of elagolix in combination with E2/NETA.

4.0 Study Objectives

The objectives of this study are to:

1. Assess the safety of elagolix 300 mg administered twice daily (BID) in combination with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) compared to placebo at 12 months in premenopausal women with heavy menstrual bleeding associated with uterine fibroids,
2. Characterize the impact of elagolix 300 mg BID with E2/NETA on bone mineral density (BMD) in women with HMB associated with uterine fibroids after up to 48 months of treatment.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included throughout the protocol.

The investigator should contact the TA MD before discontinuing a subject from the study for a reason other than "planned per protocol," (refer to Section 5.4) to ensure all acceptable mitigation steps have been explored.

This Phase 3b, randomized, sequential 12-month double-blind placebo-controlled, 36-month open-label, multi-center study is designed to evaluate the safety of elagolix with add-back therapy in women with HMB associated with uterine fibroids.

Approximately 500 subjects will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

1. Elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) (n = 335) for 48 months
2. Placebo (n = 165) for 12 months

Subjects randomized to elagolix 300 mg BID plus E2/NETA in the 12-month Treatment Period will receive the same treatment during the open-label Treatment Period. Subjects randomized to placebo in the 12-month Treatment Period will switch to elagolix 300 mg BID plus E2/NETA during the open-label Treatment Period after completing the 12-month Treatment Period.

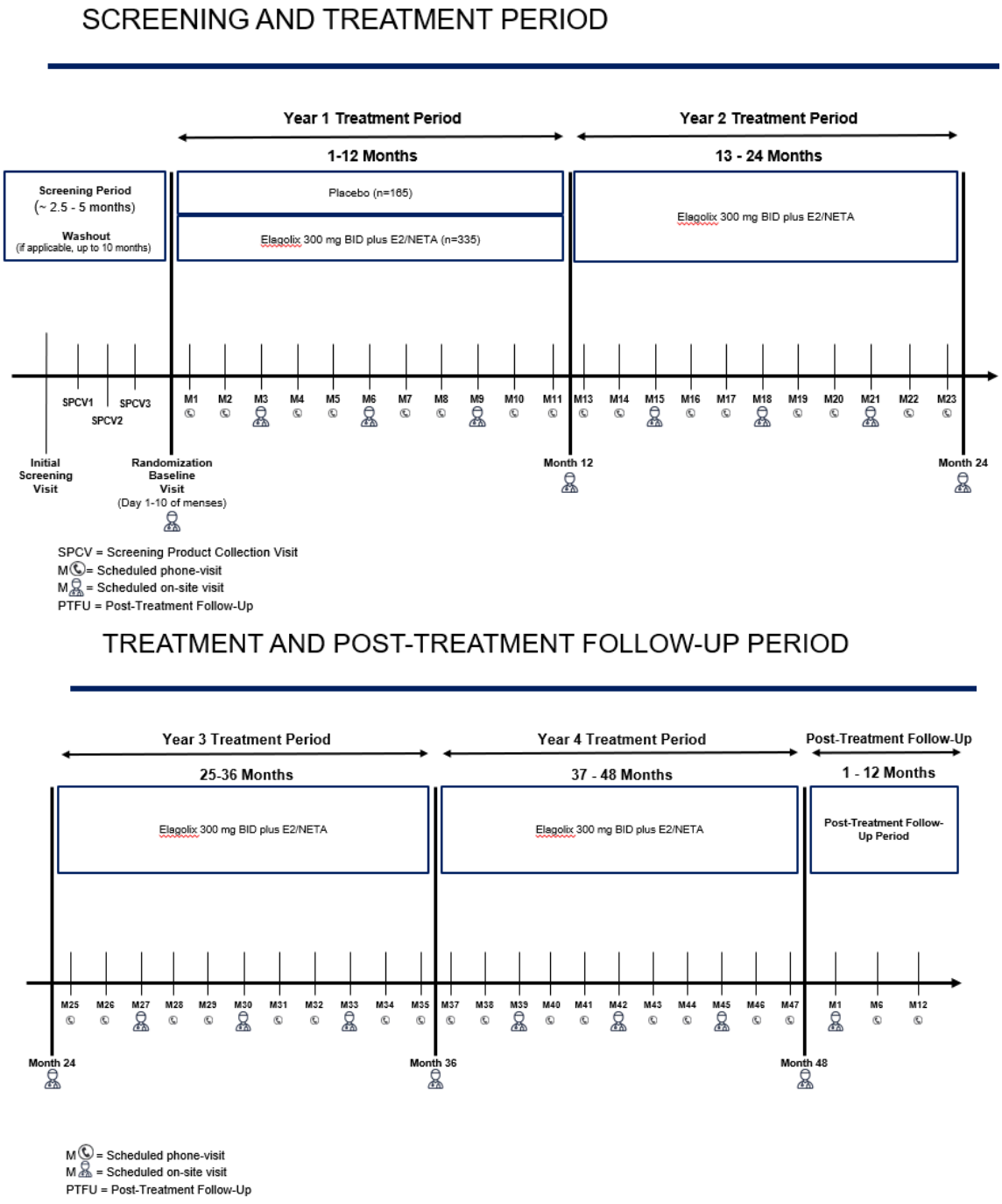
The study was designed to enroll approximately 500 subjects across approximately 175 clinical study sites to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, 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 77 months, consisting of the following 4 study periods:

1. 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).

2. Screening Period – approximately 2.5 to 5 months prior to first dose of study drug.
3. Treatment Period – up to 48-month treatment duration
4. Post-Treatment Follow-Up Period – up to 12 months duration following the last dose of study drug. Subjects are expected to enter Post-Treatment Follow-Up after completing Treatment Period Month 48, or at any time a subject prematurely discontinues during the Treatment Period.

The Study Schematic is shown below in Figure 1.

Figure 1. Study Schematic



Washout Period

Following informed consent, subjects who have been taking exclusionary medications such as hormonal medications or antifibrinolytics must enter the Washout Period to discontinue medications that may confound efficacy analyses and which must be completed prior to the Screening Period. The duration of the required washout period is based on the excluded medication that the subject had been 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 then have at least 1 menses (refer to Table 2) prior to entering the Screening Period. A pelvic ultrasound (transabdominal [TAU] and transvaginal [TVU]) may be performed prior to the Washout Period to establish the presence of a qualifying fibroid(s) or measure the uterine volume to avoid the subject unnecessarily undergoing a lengthy washout of hormonal medications.

Subjects will also begin the use of dual non-hormonal contraception during the Washout Period and receive counseling on the importance of consistent, appropriate and effective use of birth control and will have contraceptives dispensed, as necessary.

Screening Period

Subjects who do not require washout will enter the Screening Period (approximately 2.5 to 5 months) and will provide written informed consent before any study-related procedures are performed. Subjects will undergo screening procedures as outlined in Appendix C, Study Activities and described in Section 5.3.1.1, to establish eligibility based on inclusion and exclusion criteria.

A pelvic ultrasound (TAU and TVU) will be performed during screening, if not performed in the Washout Period, to determine the presence and size of qualifying uterine fibroids and uterine volume and to rule out exclusionary criteria. A saline infusion

sonohysterography (SIS) will be conducted to rule out exclusionary gynecological disorders such as intracavitary submucosal pedunculated fibroids and endometrial polyps.

Subjects who have qualifying uterine fibroids and uterine volume as assessed by ultrasound and have SIS images but are unable to fully assess the endometrial cavity after 2 separate SIS attempts have been made, may undergo an MRI for further evaluation during Screening (per imaging vendor request).

Subjects with previous invasive testing (e.g., endometrial biopsy, pelvic ultrasound, Pap test and SIS) in addition to DXA assessments within the last 3 months prior to screening and original results available may qualify to participate in this study.

Eligibility based on MBL (> 80 mL for each of 2 menstrual cycles) will be established using the alkaline hematin method. Sanitary products and the collection kits will be dispensed during Screening. Training will be provided to subjects to ensure collection of sanitary products for menstrual bleeding assessment at the start of the subject's first menses in the Screening Period (Screening Menstrual Cycle 1). Subjects will be required to collect all used or worn sanitary products (including products with no visible blood on them) on days with menstrual bleeding or spotting over the course of 2 or 3 menstrual cycles during Screening to determine eligibility for entry into the Treatment Period. Sanitary products will be returned to the site within approximately 5 days after cessation of menses for each menstrual cycle at a Screening Product Collection Visit.

Reminders regarding the consistent use of acceptable forms of dual non-hormonal birth control and collection of all used or worn sanitary products on days with bleeding or spotting will be provided on a routine basis by the Study Staff.

Subjects who have signed the informed consent and did not randomize because they either did not complete the Washout Period (if applicable), did not complete the study-specific procedures during the Screening Period (e.g., TAU/TVU or SIS) 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 in the electronic Case Report Form (eCRF).

Subjects who screen fail for this study or other AbbVie studies may be re-screened with the TA SD's approval.

Screening Sanitary Product Collection Visits

At each Screening Product Collection Visit, sanitary products to measure menstrual blood loss will be collected and a venous blood sample will be obtained. The site will submit the sanitary products and venous blood sample to the alkaline hematin laboratory for analysis of blood loss to determine eligibility.

Vital signs, a urine pregnancy test, contraception counseling and adverse event and concomitant medication review will also be performed during these visits. Additional sanitary collection kits and contraceptives will be dispensed at each on-site visit.

Year 1 Treatment Period

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

Subjects will be randomly assigned (in a 2:1 ratio) to receive either elagolix 300 mg BID plus E2/NETA (n = 335) or placebo (n = 165). The first dose of study drug will be administered at the study site on Day 1 (whether subject has a morning or afternoon visit scheduled). The subject will take her second dose on the first day that evening according to instructions. Thereafter, subjects will be instructed to 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 throughout the 12-Month Year 1 Treatment Period. Subjects entering the 12-month Treatment Period will have on-site visits at Day 1 and Months 3, 6, 9 and 12. Phone visits will be made at Months 1, 2, 4, 5, 7, 8, 10, and 11.

A urine pregnancy test will be performed at each visit throughout the 12-month Treatment Period. 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.

During the phone visits, site staff will assess ongoing adverse events, concomitant medications (if applicable), obtain the results of the subject's self-administered urine pregnancy test, and remind subjects of the importance of consistent use of appropriate and effective use of dual non-hormonal contraception.

A pelvic ultrasound (TAU and TVU) will be performed during the Treatment Period as outlined in Appendix C, Study Activities.

Subjects who prematurely discontinue at any time during the 12-month Treatment Period will be asked to complete Premature Discontinuation procedures as outlined in Appendix C, Study Activities Table and will enter the Post-Treatment Follow-Up Period.

Year 2, 3 and 4 (Open-Label) Treatment Period

Eligible subjects, who complete the 12-month Year 1 Treatment Period, will continue participation in the 36-month open label Treatment Period. Subjects randomized to elagolix 300 mg BID plus E2/NETA or placebo in the 12-month Treatment Period will receive elagolix 300 mg BID plus E2/NETA during the open-label Treatment Period.

For subjects entering the open-label Treatment Period, visits will occur either by phone or on-site as outlined in Appendix C, Study Activities.

Subjects may begin taking hormonal contraceptive preparations only after completing the open-label Treatment Period and has a negative urine pregnancy test after 1 month off of study drug and return to menses.

Post-Treatment Follow-Up Period

Subjects will enter the Post-Treatment 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 any time during the Treatment Period will enter the Post-Treatment Follow-Up Period.

Adverse event collection and concomitant medication review is detailed in Section 6.1.4 and Appendix C.

DXA scans and additional detail regarding study procedures during the Post-Treatment Follow-Up Period is provided in Section 5.3.1.1 and Study Activities, Appendix C.

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided for certain procedures. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, study visits may be conducted over the phone where feasible and AbbVie should be notified.

Visit Windows

Visit windows will be allowed during the Treatment and Post Treatment Follow-Up Periods. Each subsequent visit during the Treatment Period (Months 1 through 48) should be scheduled based on the date of the Day 1 (Randomization) visit.

Specific assessment-related visit windows are allowed. Please refer to Table 1, Visit and Assessment Windows, for assessment-specific visit windows.

Table 1. Visit and Assessment Windows

Study Visit Windows	
Study Visit	**Visit Windows**
Day 1: • Days 1 – 10 of the start of menses	No visit windows*
Treatment Periods: • Onsite Visits • Phone Visits	± 4 days
Post-Treatment Follow-Up Period: • Up to 12 Months	± 7 days
Assessment-Specific Windows for Treatment Periods	
Study Visit/Assessment	**Visit Windows**
Year 1 Treatment Period	
Month 6: • DXA Scan	–15 or + 4 days
Month 12: • Ultrasound • DXA Scan • Endometrial Biopsy** • Mammogram	
Year 2 Treatment Period	
Month 18: • DXA Scan	–15 or +4 days
Month 24: • Ultrasound • DXA Scan • Pap Test*** • Endometrial Biopsy** • Mammogram	

Table 1. Visit and Assessment Windows (Continued)

Year 3 Treatment Visit	
Month 30: • DXA Scan	–15 or +4 days
Month 36: • Ultrasound • DXA Scan • Endometrial Biopsy (regardless of TVU findings) • Mammogram	
Year 4 Treatment Visit	
Month 42: • DXA Scan	–15 or +4 days
Month 48: • Ultrasound • DXA Scan • Pap Test*** • Endometrial Biopsy (regardless of TVU findings) • Mammogram	
Post-Treatment Follow-Up Period	
Post-Treatment Follow-Up Month 6: • DXA Scan	–15 or + 4 days
Post-Treatment Follow-Up Month 12: • DXA Scan	

* Randomization must occur between Days 1 – 10 of the onset (first day of full menstrual flow) of menses.

** Not required if the TVU findings indicate an endometrial thickness < 4 mm.

*** If Pap test to be performed 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.

5.2 Selection of Study Population

Premenopausal female subjects (aged 18 to 50 years, inclusive) with HMB (> 80 mL blood loss per menstrual cycle) associated with uterine fibroids who meet the inclusion

criteria and do not meet any of the exclusion criteria will be eligible for randomization into the study.

Each Investigator will employ their clinical judgment in conjunction with protocol specified inclusion/exclusion criteria to determine if subject meets eligibility. Questions should be directed to the AbbVie Therapeutic Area Scientific Director (TA SD) listed on the title page if further clarification is required.

Due to the long Screening Period, eligibility should be assessed throughout the Screening Period and just prior to Randomization to ensure that subject continues to meet eligibility.

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 any study-specific procedures including washout or screening procedures.
2. Subject is a premenopausal female 18 to 50 years of age at the time of Screening.
3. Subject has a diagnosis of uterine fibroids documented by a Pelvic Ultrasound (TAU, TVU) assessed by a central reader and verification that a uterine fibroid meets at least one of the following criteria:
   - Intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter)
   - Subserosal fibroid ≥ 4 cm (longest diameter)
   - Multiple fibroids with a total uterine volume of ≥ 200 cm^3 to ≤ 2,500 cm^3
4. Subject has HMB associated with uterine fibroids as evidenced by MBL > 80 mL during each of two menses in Screening as measured by the alkaline hematin method.
5. Subject has a Screening FSH level of < 35 mIU/mL (35 IU/L).

6. 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.

7. Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Washout (if applicable), Screening, Treatment Periods and through the end of Month 1 of the Post-Treatment Follow-Up Period. Acceptable methods of dual contraception include the following combinations:

   - Condom with spermicide (foam, gel or polymer film)
   - Diaphragm with spermicide (condom may or may not be used)
   - Cervical cap with spermicide (condom may or may not be used)

   Subject is not required to use dual contraception methods if:

   - Sexual partner(s) is 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 dual non-hormonal contraception.
   - Subject had a bilateral tubal ligation or bilateral tubal occlusion, at least 4 months prior to 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.

8. Subject has an adequate endometrial biopsy performed during Screening, the results of which show no clinically significant endometrial pathology.

9. Subject ≥ 39 years of age at the time of randomization has a normal mammogram (BI-RADS Classification 1 to 3 or equivalent) during Screening or within 3 months prior to Screening.

10. Subject must agree to the Washout Intervals for hormonal therapies, including any other medication that may require washout as specified in Section 5.2.3.1.

11. Subject has not taken exclusionary hormonal therapies within the specified washout interval as specified in Section 5.2.3.1 prior to the initiation of any screening procedures and must have at least 1 menses prior to initiation of any screening procedures.

Rationale for Inclusion Criteria:

1	This is standard criterion in accordance with harmonized Good Clinical Practice (GCP).
2 – 5	These criteria were selected to ensure an appropriate subject population of premenopausal women with HMB associated with uterine fibroids
6, 7	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
8 – 9	These are standard criteria to ensure general good health and the safety of the subjects
10, 11	To avoid bias for the evaluation of safety by concomitant use of other medications

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if she meets any of the following criteria:

1. Subject has had menstrual cycles that are > 38 days in length for the past 3 consecutive months prior to Screening.
2. Subject has screening pelvic ultrasound or SIS results that show clinically significant gynecological findings such as:
   - A persistent simple ovarian cyst > 5 cm in longest diameter (if the pelvic ultrasounds shows a simple ovarian cysts > 5 cm and ≤ 7 cm, an ultrasound of

the ovaries may be repeated in approximately 4 - 6 weeks; however, the results must be evaluated prior to Day 1 and not meet exclusion).

- A complex ovarian cyst > 3.5 cm in diameter (longest diameter)
- An endometrioma > 3.5 cm in diameter (longest diameter)
- Large endometrial polyp (≥ 1 cm)
- Intracavitary Submucosal pedunculated fibroid

3. Subject had a myomectomy, uterine artery embolization or high intensity focused ultrasound (HIFU) within 6 months prior to Screening.
4. Subject had an endometrial ablation within 1 year prior to Screening.
5. Subject ≥ 21 years of age at Screening (or age at which Pap smears are routinely performed according to local guidelines) has a Pap smear result that meets exclusionary criteria as indicated in Figure 2, Pap Test Eligibility.
6. Subject has active pelvic inflammatory disease (PID).
7. Subject's weight exceeds the limit of the DXA machine used for this study.
8. Subject's hemoglobin level is < 7 g/dL (subjects with initial screening hemoglobin results < 7 g/dL can be prescribed iron supplements and have their hemoglobin levels retested prior to Day 1).
9. Subject had two or more blood transfusions (separate events) within 9 months prior to Screening or required a blood transfusion within 60 days prior to Day 1.
10. Subject has clinically significant abnormalities in clinical chemistry, hematology, or urinalysis (excluding findings that are associated with the disease under study such as low hemoglobin or low hematocrit) or a serum creatinine > 2.0 mg/dL at Screening. Clinically significant laboratory abnormalities may be retested prior to Day 1; however the results must meet entry criteria to be eligible for randomization.
11. Subject has aspartate aminotransferase (ASAT/SGOT) or alanine aminotransferase (ALAT/SGPT) ≥ 3.0 times the upper limit of the reference range or bilirubin

(unless known diagnosis of Gilbert's disease) ≥ 2.0 times the upper limit of the reference range.

12. 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).

13. Subject has clinically significant abnormal ECG.

14. Subject is less than 6 months post-partum, post-abortion, post-pregnancy, or post lactation at the time of entry into the Screening Period, is pregnant or breastfeeding or is planning a pregnancy within the next 48 months.

15. Subject was diagnosed with a hereditary blood coagulation disorder (e.g., Von Willebrand disease, Factor V Leiden), or has a history of surgery-related severe bleeding or severe and prolonged bleeding associated with dental work.

16. Subject has a history of osteoporosis **or** other metabolic bone disease, including:
    - Screening DXA results of the lumbar spine (L1 – L4), femoral neck, or total hip BMD corresponding to 2.0 or more standard deviations below normal (T-score ≤ –2.0)
    - Intercurrent bone disease (e.g., osteomalacia, osteogenesis imperfecta, etc.)
    - Condition that would interfere with obtaining adequate DXA measurements (e.g., history of spinal surgery, spinal hardware or severe scoliosis).
    - History or presence of a condition that is associated with a decrease in BMD (e.g., uncontrolled hyperthyroidism, uncontrolled hyperparathyroidism, anorexia nervosa) or requires chronic treatment with systemic corticosteroids.
    - History of low-trauma bone fractures (e.g., fracture resulting from a fall from a standing height or lower)
    - Bilateral hip replacement
    - Clinically significant hypocalcemia, hypo- or hyperphosphatemia
    - Treatment with medication (excluding calcium and vitamin D) for bone disease associated with a decrease in BMD

17. Subject has a history of major depression or post-traumatic stress disorder (PTSD) episode within 2 years of Screening, OR a history of other major psychiatric disorder at any time (e.g., schizophrenia, bipolar disorder).

18. 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.

19. 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 the 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 or symptomatic endometriosis [confirmed by laparoscopy/laparotomy]).

20. Subject has active vein thrombosis, pulmonary embolism or history of these conditions.

21. Subject has active arterial thromboembolic disease (e.g., stroke, myocardial infarction) or history of these conditions.

22. Any history of or active malignancy (except basal cell carcinoma of the skin) with or without systemic chemotherapy.

23. Subject has hypersensitivity, documented allergy to or is unable to tolerate norethindrone, norethindrone acetate or estradiol, or these preparations (e.g., Activella) or are otherwise intolerant of the estrogens or progestins in hormonal contraceptives or contraindicated for medical reasons.

24. Subject has a surgical history of:
    - Hysterectomy (with or without oophorectomy)
    - Bilateral oophorectomy
    - Bariatric surgical procedures of any type within 6 months of Screening
25. Subject is using a copper intra-uterine device (CU-IUD) or levonorgestrel intra-uterine system (LNG-IUS). If the LNG-IUS is removed and subject completes washout per Section 5.2.3.1, or the CU-IUD is removed and the subject returns to 1 menses, the subject can be screened for eligibility to be considered for randomization.
26. 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, intranasal or intra-articular injectable (for occasional use) corticosteroids are allowed.
27. Subject is using oral retinoid preparations such as Accutane® (isotretinoin). Topical isotretinoin applications are permitted.
28. Subject has a history of drug abuse and/or alcohol abuse within 12 months prior to Screening that may affect the safety, data collection, or have an adverse effect on the study participation.
29. Subject previously received Elagolix/an investigational GnRH antagonist less than 1 year prior to entry into the Screening period.
30. Subject is currently participating in another investigational study (drug or device) or has participated in an investigational drug study (i.e., receiving or has received investigational product) within 1 month or five times the investigational drug half-life, whichever is longer, prior to Screening procedures. If a subject has participated in an investigational trial with hormonal treatment, the washout interval specified in Section 5.2.3.1 applies.

31. Subject, who in the judgment of the investigator, will be unable or unwilling to comply with study-related assessments and procedures, including collection of sanitary products and consistent use of dual non-hormonal contraception throughout the required time period.

Rationale for Exclusion Criteria:

1 – 4, 24	These criteria were selected to ensure an adequate subject population of women with HMB and uterine fibroids and no clinically significant gynecological disorders
5 – 13, 15 – 23, 28	These are standard criteria to ensure general good health and the safety of the subjects
14	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 adequate precautions are taken to avoid pregnancy or breastfeeding while receiving elagolix
25 – 30	These criteria were selected to ensure that safety can be adequately assessed
31	This criterion was added to ensure the population of subjects enrolled will comply with study-related procedures and subject collection requirements throughout the entire study

5.2.3 Prior and Concomitant Therapy

Any medication administered to treat uterine fibroid symptoms or HMB associated with uterine fibroids within 6 months prior to Washout or Screening must be recorded in source documents and the eCRFs. The date(s) of administration (including start and stop dates), dose, route, and reason for use and discontinuation must be recorded in source documents and on the Prior Uterine Fibroid Medication eCRFs.

Please refer to Section 5.2.3.2 for details regarding concomitant medication use.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

5.2.3.1 Prior Hormonal/Anti-Hormonal Medications

Subjects using hormonal contraception or other hormonal/anti hormonal therapies may be considered for study participation provided they complete the required washout. Subjects must have at least 1 menses after completion of Washout before entering into the Screening Period. Subjects currently using hormonal/anti-hormonal therapies will sign an ICF before they discontinue the hormonal medication. 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 required washout. 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.

Subjects entering washout will be required to undergo study specific procedures, as outlined in Appendix C, Study Activities.

Subjects using an LNG-IUS, who agree to have the LNG-IUS removed, must complete the washout period and have at least 1 menses during the washout prior to Screening. Subjects using a CU-IUD, who agree to have the IUD removed may also enter screening (no washout required) and must have at least 1 menses after removal of the CU-IUD prior to collecting sanitary products for assessment of menstrual blood loss as the removal of the CU-IUD may cause abnormal menstrual bleeding that may interfere with the assessment of eligibility criteria and also to ensure there is no pregnancy.

The minimum washout intervals for hormonal medications (including LNG-IUS) prior to Screening are described in Table 2. If the type of hormonal product and the length of Washout Period are not listed in the table below, consult the AbbVie TA MD.

Table 2. Washout Intervals for Exclusionary Hormonal/Anti-Hormonal Therapy

Therapy	Minimum Interval for Washout**	Number of Menses Required AFTER Completion of Washout Period (Prior to Initial Screening Visit)
Medroxyprogesterone acetate injection (Depo-Provera®; Sayana®)	300 days from injection	2 menses
GnRH agonist 3 month depot (Lupron Depot® 11.25 mg), goserelin acetate (Zoladex®)	180 days from injection	1 menses
Synarel® (Nasal Spray) Nafarelin acetate GnRH agonist – 1 month depot (including Lupron Depot® 3.75 mg)	120 days	
Non-oral GnRH antagonist	90 days	
Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate, Vilaprisan)		
Danazol (Cyclomen®)		
Aromatase inhibitors		
Oral contraceptives***	30 days	
Oral, transdermal or intravaginal estrogen preparations*		
Oral, intravaginal or transdermal progesterone/progestin preparations, including tibolone*		
Hormonal, sub-dermal progestin implant (e.g., Nexplanon®)	30 days after removal	
NuvaRing®		
Moderate or strong inducers (e.g., cyclosporine, rifampin, carbamazepine, St. John's Wort) of cytochrome P450 3A (CYP3A)	30 days prior to randomization	
Antifibrinolytics	2 weeks	

* E2/NETA will be taken by subjects randomized to the E2/NETA treatment group. Exception: levonorgestrel 1.5 mg or ulipristal acetate 30 mg used for emergency contraception.

** This is the minimum washout; however, subjects may not enter Screening until at least 1 menses (or at least 2 menses for Medroxyprogesterone acetate injection) has occurred after completion of the Washout Period. If less than a full course of therapy is administered, the investigator should contact the AbbVie TA MD listed in Section 6.1.5 to discuss and confirm the required washout interval.

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

5.2.3.2 Concomitant Therapy

All other medications or vaccines (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of entering into the Washout Period (if required) or Screening Period and during the Treatment and Post-Treatment Follow-Up Periods must be recorded in source documents and on the Concomitant Medication eCRFs. The reason for use, date(s) of administration (including start and end dates) and dosage information (including dose and frequency) must be recorded.

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be administered during the Treatment and Post-Treatment Follow-Up Periods, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

5.2.3.3 Iron Supplementation

Excessive blood loss from heavy menses may result in iron deficiency anemia. Iron deficiency anemia is defined by the World Health Organization (WHO) as an Hgb concentration below 12 g/dL (120 g/L) for non-pregnant women. Subjects entering the study with anemia or who develop anemia during the study, if not already taking iron supplements, should be prescribed iron supplementation by the Investigator, as per standard of care. If the Investigator does not prescribe iron supplements for subjects with a Hgb < 12g/dL, the reason should be documented in source documents.

The recommended oral dose of ferrous sulfate is 300 to 325 mg following the diagnosis of anemia. During Screening, all subjects with an Hgb level < 7 g/dL will be retested after receiving iron supplements; these subjects will only be eligible to randomize if their Hgb results meet eligibility prior to Day 1 (Randomization) and has not required a blood transfusion within 60 days prior to Day 1. If a subject is unable to tolerate ferrous sulfate

then ferrous gluconate, liquid iron or intravenous (IV) iron may be prescribed. If subjects experience constipation from iron supplement use, stool softeners may be prescribed. All iron supplements taken during the study, from Screening through the final visit, must be recorded on the concomitant medications eCRF.

Further instructions on the provision of iron supplementation and stool softeners will be provided separately from this protocol.

5.2.3.4 Concomitant Use of Corticosteroids

Chronic use (> 14 days) of systemic corticosteroids is prohibited during the Washout, Screening and Treatment Period, however inhaled corticosteroids for the treatment of asthma are permitted. Over-the-counter and prescription topical, inhaled, intranasal or intra-articular injectable (for occasional use) corticosteroids are allowed. Subjects, who based on medical history, may potentially require long-term oral treatment with corticosteroids during the course of the study, should not be enrolled. If the subject requires systemic corticosteroid use for > 14 days, the AbbVie TA MD must be notified.

5.2.3.5 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 the Washout, Screening, Treatment Periods and until the Post-Treatment Follow-Up Period Month 1. Subjects may start hormonal contraception after completion of Post-Treatment Follow-Up Period Month 1, and having a negative urine pregnancy test after 1 month off of study drug and returned to menses. If the Subject has not returned to menses by Month 1 in the Post-Treatment Follow-Up Period, the Investigator would use acceptable medical practice to reinitiate hormonal contraceptive (e.g., pregnancy test, FSH, induction of withdrawal bleed, etc.).

For subjects who are prescribed/administered the emergency contraceptive pill during the study, the information should be captured in the source documents and eCRF and the AbbVie TA MD must be informed.

Tranexamic acid should not be taken during the Screening and Treatment Periods, however tranexamic acid, if necessary, can be prescribed following completion of the Treatment Period and the subject has returned to first full menses. Should the subject be prescribed tranexamic acid during the Treatment Period, they will be discontinued and will enter the Post-Treatment Follow-Up Period.

Any supplements or herbal remedies used to treat premenstrual or gynecological problems, such as black cohosh, are excluded.

The following medications should not be taken during the Washout (if applicable), Screening, and the Treatment Periods.

Table 3. Prohibited Medications

Prohibited During the Washout, Screening, Treatment and Post-Treatment Follow-Up Periods	
GnRH agonist	Leuprolide acetate (Lupron®)
Prohibited During the Washout, Screening and Treatment Periods and Through Follow-Up Month 1	
Hormonal and Non-hormonal Estrogen Supplements,% such as:	GnRH agonists: nafarelin acetate (Synarel®), goserlin acetate (Zoladex®) GnRH antagonists (other than study elagolix) Danazol (Danocrine®, Cyclomen®) Medroxyprogesterone acetate (Depo-Provera®, Provera®) Oral contraceptives Estrogen preparations* Testosterone preparations Other progestins* (oral, vaginal, transdermal, implantable, IUD, or LNG-IUS, except emergency contraception) HCG or HCG products Glucocorticoids, oral or injectable (chronic use only) Other progestins (oral, vaginal, IUDs, implantable) Levonorgestrel (except emergency contraception, i.e., levonorgestrel 1.5 mg) Mifepristone Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate (except as emergency contraception, i.e., 30 mg) and Vilaprisan) 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)
Antifibrinolytics%	Tranexamic acid (Lysteda, Cyklokapron, Cyclo-f)

Table 3. Prohibited Medications (Continued)

Prohibited During the Washout, Screening, and Treatment Periods	
Moderate or strong CYP3A Inducers,[7] and Anti-epileptic medications, such as:	**Strong Inducers:** St. John's Wort Rifampin Carbamazepine Phenytoin Dexamethasone chronic use **Moderate Inducers:** Bosentan Efavirenz Etravirine Modafinil Nafcillin
Strong organic anion transporting polypeptide 1B1 (OATP1B1) inhibitors such as:	Cyclosporine Rifampin (single dose)
Prohibited During the Screening, Treatment, and Post-Treatment Follow-Up Periods	
Osteoporosis Medications Bisphosphonates, RANKL, [Receptor activator of nuclear factor-κ B ligand] inhibitors, Anabolic Bone Agents or rPTH, such as:	Denosumab, Teriparatide Fosamax®, Fosamax Plus D®, Binosto®, Boniva®, Reclast®, Zometa®, Prolia®, XGEVA®, Forteo®, Actonel®, Atelvia®, Miacalcin®, Fortical®
Synthetic Prostaglandin E1 (PGE1) Analogs, such as:	Misoprostol (Cytotec®, Arthrotec®) Single use of PGE1 for cervical preparation prior to biopsy is allowed; chronic use is prohibited
Glucocorticoids/Corticosteroids, systemic administration (oral, IM or IV)	*Except for short-term use as noted in this protocol.*
Oral Retinoids (topical applications are permitted), Teratogens such as:	Topiramate, Accutane® (isotretinoin) and other oral retinoids

* E2/NETA will be taken by subjects randomized to the E2/NETA dose group.

\# Due to the extensive list of herbal remedies and supplements, please contact the AbbVie TA MD for any that may be prohibited.

% Subjects may begin the use of hormonal contraceptives following completion of the Treatment Period and must have a negative urine pregnancy test 1 month off of study drug and return to menses. Tranexamic acid, if necessary can be prescribed following completion of the Treatment Period and the subject has returned to first full menses.

If a prohibited medication is necessary to treat an adverse event or a pre-existing condition other than uterine fibroids, the AbbVie TA MD noted on the title page should be consulted; however, if clinically required and to prevent an immediate hazard to the subject being treated, the AbbVie TA MD should be notified as soon as possible after the start of use. Additionally, if a subject takes a prohibited medication during the study, except as permitted per protocol, her continued participation in the study will be evaluated by the Investigator and the AbbVie TA MD. If there are any questions regarding prior or concomitant therapy, please contact your Study Monitor.

5.2.4 Contraception Recommendations

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 Post-Treatment Follow-Up Period. Subjects may begin the use of hormonal contraception (e.g., oral or IUD) after completion of the Post-Treatment Follow-Up Month 1 visit and has a negative urine pregnancy test after 1 month off study drug and return to menses.

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

- Condom with spermicide (foam, gel or polymer film)
- Diaphragm with spermicide (condom may or may not be used)
- Cervical cap with spermicide (condom may or may not be used)

Subjects are not required to use dual contraception methods if:

- Sexual partner(s) is 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
- Subject had a bilateral tubal ligation or bilateral tubal occlusion at least 4 months prior to 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 has begun the use of hormonal contraception after the Post-Treatment Follow-Up Month 1 visit.
- Subjects may begin the use of hormonal contraception after the Post-Treatment Follow-Up Month 1 visit, provided she has a negative urine pregnancy test 1 month off of study drug and has returned to menses. If the Subject has not returned to menses by Month 1, the Investigator would use acceptable medical practice to reinitiate hormonal contraceptive (e.g., pregnancy test, FSH, induction of withdrawal bleed).

The following measures will be taken to help ensure 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 dual 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 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 should only use the pregnancy prevention materials provided by the Sponsor as these products have undergone analytical testing by the analytical lab to confirm there is no or limited interference with the alkaline hematin method.
   - Subjects will be allowed to choose an acceptable contraception method of their choice from the contraceptives 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 the 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 Washout, if applicable, Screening and Treatment Periods, as needed.
   - The source documents will capture 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, use of a non-study supply brand, 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. On-site and phone visits are used to promote frequent interaction with site staff and opportunities for continued education.
5. At each Treatment Period visit (on-site and phone visits), the proper use of contraception will be reinforced to address possible ineffective use and the risk of unexpected pregnancy due to unprotected sexual activity.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the contraception counseling should be conducted during the phone visits (as applicable). The site should ship a reasonable quantity of contraceptive supplies for subject use until next on-site visit. The type and quantity of contraceptives shipped to the subject must be documented along with the shipping tracking number and documentation. When subject is able to go to the site, site should make sure that enough contraceptives are dispensed to the subject.

5.3 Efficacy, Pharmacokinetic, Biomarker, Optional Exploratory Research Samples and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures during the Washout (if applicable), Screening, Treatment and Post-Treatment Follow-Up Periods described in this protocol are summarized 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 monitoring study drug 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 eCRFs with the exception of the select ePRO data and data from the central lab/imaging vendor.

The Screening Period will occur within approximately 2.5 to 5 months prior to administration of the first dose of study drug on Day 1 (Randomization). For procedures performed during the Screening Period and subsequently repeated (as allowed per protocol or at the discretion of the AbbVie TA SD), the procedure performed closest to dosing will serve as a baseline for clinical assessment.

Study procedures during the Treatment and Post-Treatment Follow-Up Periods should be performed within the visit windows specified in Table 1. Scheduled monthly visits during the Treatment and Post-Treatment Follow-Up Periods are based on a 28-day month.

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 SD or 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.

Due to the long Screening Period, eligibility should be assessed throughout the Screening Period, including just prior to randomization to ensure that the subject continues to meet eligibility and that the results from all screening procedures are available prior to randomization.

Informed Consent

The IRB/IEC approved informed consent will be signed by the subject before beginning any study-specific procedures or discontinuing any hormonal contraception/therapies or other prohibited medications. Exploratory research testing is optional and a subject must be provided a separate informed consent option for this blood collection. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical/Social History

A complete medical history, including documentation of any clinically significant medical conditions and medications, history of tobacco and alcohol use, and 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/Obstetrical and Uterine Fibroid History

A detailed gynecological/obstetrical and uterine fibroid history will be collected either during the Washout Period (if applicable) or during the Screening Period for those who do not require washout, and will include the following:

- History of uterine fibroids, including year of diagnosis and uterine fibroid symptoms
- History of endometriosis, ovarian cysts, endometrial polyps, or other relevant gynecological conditions
- History of gynecological surgeries and gynecological diagnostic procedures
- History of bleeding including average cycle length and average number of days with bleeding/cycle over the last 6 months and typical intensity of menstrual periods
- History of irregular bleeding or prolonged bleeding

- Prior hormonal medications including those taken for treatment of uterine fibroids or other gynecological conditions
- Prior use of non-hormonal medications for the treatment of uterine fibroids, including dates of use for 6 months prior to either Washout (if applicable) or Screening
- History of sexually transmitted infections
- Obstetrical History
- Pregnancy history including:
    - Total number of pregnancies
    - Number of live births
    - Number of abortions (including elective, therapeutic and spontaneous abortions)
    - Delivery outcomes (specifically, anomalies including congenital malformations and chromosomal abnormalities).

The gynecological/obstetrical and uterine fibroid history will be reviewed and should be updated if needed prior to dosing on Day 1 (Randomization) 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), Day 1 and Post Treatment Follow-Up Month 1.

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site for the physical exam, it can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

Gynecological (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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site for the gynecological exam, it can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

Vital Signs

Vital sign determination of pulse, blood pressure, respiratory rate, and body temperature will be obtained at all on-site visits during the study as indicated in Appendix C. The blood pressure and heart 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site for the vital signs, it can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

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 records at the study site.

Mammogram

A mammogram will be obtained during Screening (only for subjects who will be 39 years of age or older at the time of randomization unless the subject had a mammogram performed within 3 months prior to Screening), and at Months 12, 24, 36, 48 and

Premature Discontinuation Visit (if applicable). Local mammogram results and final interpretation must be entered into the eCRF upon receipt.

If a subject's screening 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 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 4, 5 or 6 will not be eligible for randomization into the study. Subjects 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 39 years of age or older at the time of the scheduled study visit at Months 12, 24, 36, 48 and Premature Discontinuation Visit (if applicable). A mammogram is not required for prematurely discontinued subjects if the subject had a mammogram within approximately 6 months prior to the PD 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site for the mammogram, it can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

Pap Test

Pap test will be performed on all subjects at the visits listed in Appendix C. A Pap test will be performed in subjects ≥ 21 years of age during the Screening Period, using the Thin Prep® Pap Test™ provided and analyzed by the central laboratory. If the subject is experiencing menstrual bleeding that precludes the performance of the Pap test, this procedure should be performed as soon as possible after the menstrual bleeding has ended. In the case of an unsatisfactory sample, the Pap test can be repeated. The repeat Pap test should also be performed when the subject is not experiencing menstrual bleeding. In order to be enrolled in the study, the Pap test must meet eligibility requirements as outlined in Figure 2, Pap Test Eligibility.

Subjects age 25 – 51 years old, with the Pap diagnosis of ASC-US (atypical squamous cells of undetermined significance) with high risk human papillomavirus (HPV), or low grade squamous intraepithelial lesion (LSIL) and those > 30 years of age with negative (NILM) but absent or insufficient endocervical/transformational zone component will have reflex HPV testing as outlined in Figure 2. Those with high risk HPV, LSIL with high risk HPV or LSIL negative for HPV, or subjects > 30 years of age with Negative Intraepithelial Lesion or Malignancy (NILM) but with negative or absent endocervical or transformation zone component with high risk HPV will undergo additional evaluation as outlined in Figure 2 with colposcopy and biopsy, if applicable per local guidelines or standard of care.

After colposcopy, subjects who have a histological diagnosis of CIN 1 or less with an adequate colposcopy and a negative endocervical sample post colposcopy may continue in Screening. For subjects with no lesion identified on colposcopy or when colposcopy

examination is unsatisfactory, endocervical sampling must be performed to confirm a negative/benign endocervical sample.

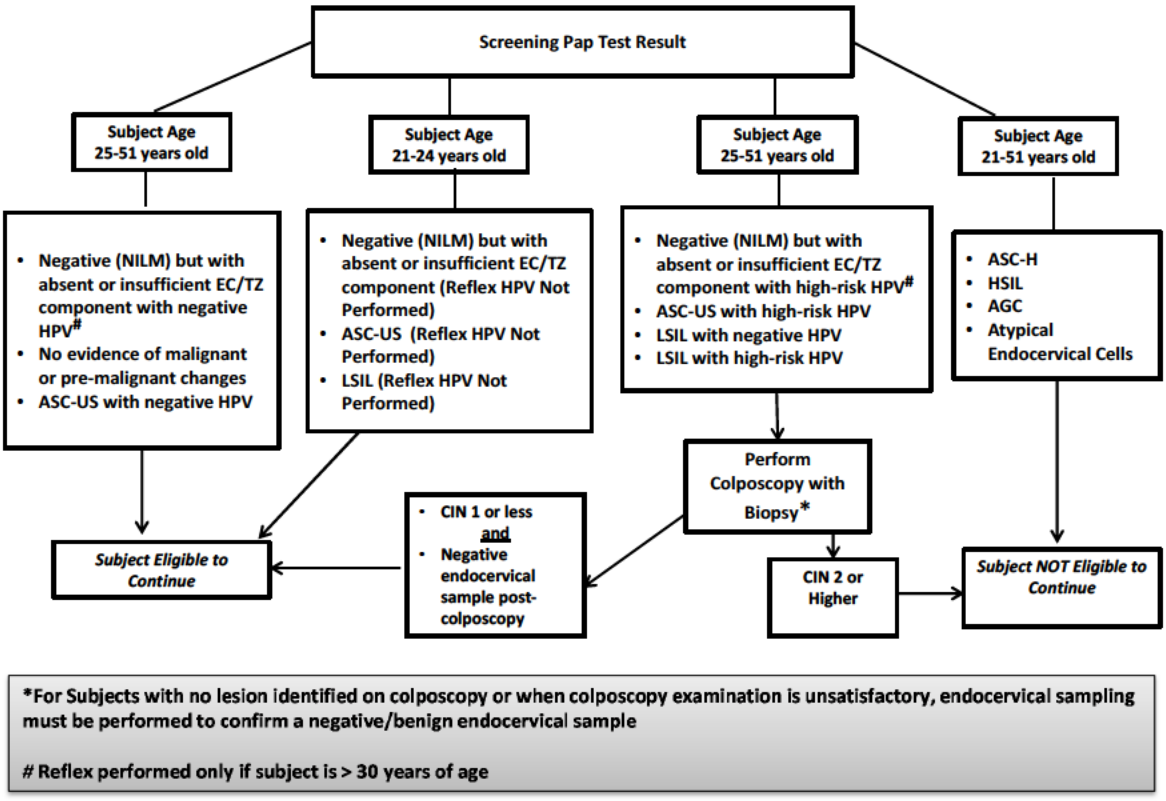
Subjects with the cytology screening result of atypical squamous cells cannot exclude HSIL (ASC-H), high-grade intraepithelial lesion (HSIL), or atypical glandular cells (AGC), atypical endocervical cells or histological diagnosis of CIN 2 or 3 are not eligible for the study.

During the Treatment Period, a Pap Test will be performed at Months 24, 48 and the Premature Discontinuation visit (if applicable). During Treatment, if the subject has an abnormal pap test that 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site for the pap test, it can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

Figure 2. Pap Test Eligibility



Endometrial Biopsy

During the Screening Period, an endometrial biopsy will be performed in all subjects.

Instructions on endometrial biopsy collection and processing procedures for shipping will be provided by the central laboratory. Sites can either use the endometrial biopsy instruments provided by the central laboratory or any other endometrial biopsy instruments available at the study site. Subjects must have a confirmed negative urine pregnancy test within 24 hours prior to undergoing the endometrial biopsy.

Pre-medication for the endometrial biopsy procedure is allowable and should be recorded in source documents and on the appropriate eCRF. At the Investigator's discretion,

misoprostol for cervical dilatation is allowable. In addition, Lidocaine may be used as local anesthesia on the cervix. Any medications used for the procedure should be recorded in source documents and on the appropriate eCRF. If there is a need for consideration for an office hysteroscopy to obtain the endometrial biopsy sample, the TA MD should be consulted.

If the endometrial biopsy is performed on the same day as the Pap smear or pelvic ultrasound, the endometrial biopsy should be performed after the Pap smear and pelvic 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 may be repeated; however, results must be available prior to randomization. Subjects must have an adequate endometrial biopsy, (i.e., results show no endometrial pathology to be eligible for randomization).

If an abnormal finding such as endometritis, 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 can be treated outside of the protocol, the subject will need to be screen failed and can be re-screened.

An endometrial biopsy is not required during the Treatment Period if the ultrasound findings at Treatment Months 12 or 24 indicate an endometrial thickness < 4 mm. If the ultrasound findings during the Treatment Period Months 12 or 24 indicate an endometrial thickness ≥ 4 mm, then the subject must have an endometrial biopsy performed at these time points.

For this amendment (Amendment 6) based upon FDA feedback, endometrial biopsy at Month 36 and 48 is required regardless of the TVU findings at the corresponding visit.

Specifically, for subjects who have completed Month 36 study visit without the endometrial biopsy, subjects should return for an interval endometrial biopsy as an Unscheduled Visit. Refer to Appendix C, Study Activities, for more information.

If the Month 12, 24, or 36 biopsy results are normal or the sample contains scant endometrium without abnormalities, the subject may continue in the remaining of the open-label Treatment Period.

In the event the Month 12 or 24 biopsy cannot be performed (e.g., due to a stenotic cervix or location of fibroids) or an insufficient biopsy sample is obtained and the concurrent TVU indicates a thickness of ≥ 4 mm, a repeat biopsy must be performed. In the event that the Month 36 or 48 biopsy cannot be performed, or an insufficient biopsy sample is obtained, a repeat biopsy must be performed.

If the repeat biopsy is performed and the results are normal or the sample contains scant endometrium without abnormalities, the subject may continue the open-label Treatment Period.

If the repeat biopsy sample cannot be obtained or remains insufficient, the AbbVie TA MD should be consulted.

An additional endometrial biopsy should be performed if clinically indicated for breakthrough bleeding, taking into account of the subject's previous biopsy results, TVU findings, patient compliance with study drugs and recognizing subjects are receiving a daily dose of progestin.

Subjects with abnormal endometrial pathology results (including, endometrial hyperplasia with or without atypia and endometrial cancer) during the Treatment Period should be discontinued and instead will enter the Post-Treatment Follow-up Period. The endometrial pathology should be managed according to standard of care.

In addition, if there is an abnormal endometrial pathology at Treatment Month 48, this should be managed according to standard of care.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site for the endometrial biopsy, it can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

Central Imaging Procedures

Fibroid and uterine assessments will be obtained using pelvic ultrasound (TAU and TVU) at Washout (if applicable), Screening, Months 12, 24, 36, 48 or Premature Discontinuation Visit and SIS at Screening. All ultrasound images will be sent to the Central Imaging Core Lab (central reader) for review to determine eligibility for randomization and to monitor safety during the Treatment Period.

The pelvic ultrasound (TAU, TVU and SIS) and MRI (if applicable) will be performed by the investigative sites' or affiliated Radiology Department. The ultrasonographer at each investigative site will be required to acquire the ultrasound, SIS and MRI (if applicable) images according to the Imaging Acquisition Guidelines provided by the central reader. Images should be sent/transmitted to the central reader to determine eligibility for entry into the study and for subject evaluation during the course of the study. Refer to the Image Acquisition Guidelines for instructions on submitting images to the central reader.

The pelvic ultrasound (TAU, TVU and SIS) and MRI (if applicable) will be assessed both locally and by the central reader. The central reader will issue an Eligibility Form based on review of the pelvic ultrasound and SIS indicating the presence or absence of a qualifying fibroid and/or uterine volume and whether any exclusionary pathology was present. If images are unevaluable, the central reader will inform the investigative site and additional images will need to be resubmitted. If there is a discrepancy between the local assessment and the central reader's assessment, this should be brought to AbbVie's attention and TA MD will discuss the findings with the local site and central reader on a case-by-case basis to determine eligibility.

The Investigator or designee should consult the local ultrasound and SIS reports and/or images in order to determine if any exclusionary criteria are present and make safety-related judgments concerning the subject. The interpretation of the local report and/or images will be filed or recorded in the subject's source documents. Data and/or local interpretation from the local ultrasound, DXA, SIS and MRI (if applicable) images will not be recorded in the eCRF.

During the Treatment and Post-Treatment Follow-Up Periods, the central reader may issue a report if any significant changes are observed that may affect subject safety during the study. In these cases, the Investigator should review the local ultrasound, SIS and/or MRI (if applicable) images and treat as per standard of care.

The pelvic ultrasound, SIS and MRI (if applicable) will be performed as outlined in Appendix C, Study Activities.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site or to the imaging facility, the DXA and TAU/TVU can be delayed up to 1 month from their scheduled time. Should the delay be longer, AbbVie should be notified.

Pelvic Ultrasound: TAU and TVU

A pelvic ultrasound (TAU and TVU) will be performed early in the Screening Period and should ideally be performed during the subject's early proliferative phase of the menstrual cycle (approximately Days 4 – 8 of the cycle), or in the Washout Period, if applicable. Subsequent pelvic ultrasounds will be performed at the time points indicated in, Appendix C, Study Activities. The pelvic ultrasound will determine the presence of qualifying uterine fibroids and uterine volume. The TAU and TVU will be used to confirm the presence of qualifying uterine fibroids (at least 1 fibroid with diameter $\geq$ 2 cm (longest diameter), or multiple fibroids with a uterine volume of $\geq$ 200 cm^3 to $\leq$ 2,500 cm^3, and to obtain measurements of the dimensions of the uterus and of the largest fibroid. The TVU will be used to assess gynecological disorders, such as ovarian

cysts and endometriomas. However, these assessments can also be made by TAU, if necessary.

Assessments for the pelvic ultrasound include, but are not limited to the following:

- Endometrial thickness
- Presence of abnormal endometrial appearance or endometrial pathology
- Presence of uterine fibroids
- Number of uterine fibroids
- Volume and location of the 3 largest fibroids
- Uterine volume in cubic centimeters
- Presence of ovarian cysts
  - Number
  - Size (cm)
  - Location (right or left ovary)
  - Simple versus complex
- Endometrioma > 3.5 cm longest diameter
- Solid ovarian lesions > 1.5 cm longest diameter

Saline Infusion Sonohysterography (SIS)

In addition to the pelvic ultrasound, an SIS will also be performed in all subjects during the Screening Period, to assess exclusion criteria based on the presence of focal intracavitary lesions including:

- Endometrial polyp ≥ 1 cm
- Intracavitary submucosal pedunculated fibroid

The SIS should be performed as early as possible during the Screening Period to rule out any exclusionary findings; for subjects entering washout, an SIS will not be performed until the subject enters the Screening Period in order to limit the number of invasive procedures prior to fully determining eligibility. The subject must have a confirmed

negative urine pregnancy test result within 24 hours prior to undergoing the SIS. It is advised that the SIS be performed post-menses to Day 10 of the menstrual cycle. Ibuprofen and antibiotics may be administered prior to conducting the SIS, if standard of care.

If a subject is known to have an endometrial polyp ≥ 1 cm, and desires to have the polyp removed outside of the study, prior to entering Screening the subject must have a negative pathology report and return to one normal menses prior to screening.

Subjects who have qualifying uterine fibroids and uterine volume as assessed by ultrasound but have SIS images that are unable to fully assess the endometrial cavity after 2 separate SIS attempts have been made, may undergo an MRI (per imaging vendor request) for further evaluation.

Intracavitary Uterine Findings

An SIS may be performed during the Treatment Period if the pelvic ultrasound (TAU and TVU) results suggest an intracavitary lesion such as a polyp. The finding of a polyp during the Treatment Period should be documented as an adverse event if the Investigator considers it to be clinically significant.

The AbbVie TA MD should be notified of the subject's management plan for any clinically significant pathologic findings during the Treatment Period.

Ovarian Findings:

During Screening, if the initial pelvic ultrasound shows a simple ovarian cyst > 5 and ≤ 7 cm in longest diameter, an ultrasound of the ovaries may be repeated in approximately 4 to 6 weeks. The repeat results must be evaluated prior to Day 1 (Randomization) and not meet exclusion criteria (i.e., persistent simple ovarian cyst > 5 cm).

In Screening, if any of the adnexal structures, such as an ovary, cannot be visualized on the pelvic ultrasound due to, for example, fibroid location and/or fibroid size, the subject

may be eligible for randomization provided there are no exclusionary findings based on an alternate imaging that can evaluate that adnexa such as an MRI (per central reader agreement).

During the Treatment Period, if the pelvic ultrasound shows a simple ovarian cyst > 5 cm or a complex ovarian cyst (including endometriomas) > 3.5 cm in longest diameter the findings should be documented as an adverse event if the Investigator considers them to be clinically significant.

Bone Mineral Density (DXA Scan)

DXA scans of the lumber spine, femoral neck and total hip will be performed by qualified technologist/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 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 T-scores and BMD % change from baseline, as applicable) of the DXA scans performed. Site training and qualifications, including assessment of instruments, will be evaluated/approved by the central reader prior to screening the first subject. 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. Sites will need to obtain approval from the central reader prior to initiating study scans.

A DXA scan will be performed during Screening Period and sent to the central reader to determine eligibility and serve as the baseline scan for subject management. Subjects with a T-score of < –2.0 at the lumber spine, total hip **or** femoral neck on the screening DXA scan will not be eligible to enter the study.

During the Treatment Period, DXA scans will be performed for all subjects 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 subject's treatment assignment (in the 12-month Treatment Period), but not to the corresponding time point.

If the results of any post-baseline DXA prior to and including Month 48, as read by the central reader selected for the study, document a T-score of < –2.5 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.

Subjects with a BMD decrease of > 8% in the lumbar spine, total hip, or femoral neck (any of the three regions) on any DXA scan performed during the Treatment Period (i.e., Months 6, 12, 18, 24, 30, 36, and 42) must be discontinued from study drug dosing and will enter the Post-Treatment Follow-Up Period.

DXA scans are also required if a subject premature discontinues for the following reasons:

- 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 unless a DXA scan has been performed within 3 months of Premature Discontinuation.

However, if a subject is being discontinued from the study due to a T-score of < –2.5 in any region (the lumber spine, total hip or femoral neck), 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 into the Post-Treatment Follow-Up Period and continue with required BMD evaluations.

DXA scans of the lumbar spine, total hip, and femoral neck will be obtained at Post-Treatment Follow-Up Period at Months 6 and/or 12, except for subjects who prematurely discontinued less than 3 months during the Treatment Period.

If the BMD percent change from baseline of any post-baseline DXA 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 location (lumber spine, total hip **or** femoral neck) that results in discontinuation from the study should be reported as an adverse event (Section 6.1.1).

Clinical Laboratory Tests

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

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/ALAT) Serum glutamic-oxaloacetic transaminase (SGOT/ASAT) Alkaline phosphatase Serum iron[1] Serum ferritin[1] Total iron binding capacity (TIBC)[1] Vitamin D Testing[1]	Specific gravity Ketones Protein Blood Glucose pH
		Lipid Panel (After Minimum 8-Hour Fast)
		Low-density Lipoprotein (LDL) cholesterol High-density Lipoprotein (HDL) cholesterol Triglycerides Total cholesterol
Pregnancy Test		**Endocrine Panel**
Serum pregnancy (only completed if urine pregnancy test is positive)		Follicle-stimulating hormone (FSH) Reflexive Thyroid Stimulating Hormone (TSH)

1. To be completed at Screening visit only.

Laboratory samples indicated in Table 4 will be assessed using a certified central laboratory selected for this 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 vital signs and ECG recording are conducted at a visit.

Clinical chemistry samples should be obtained in the morning following an overnight fast (minimum of 8 hours); however, there may be circumstances when the sample is obtained later in the day and/or not under fasting conditions. If the sample was obtained with 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, with the exception of the venous blood sample for alkaline hematin analysis which will be sent to the Alkaline Hematin Laboratory during screening.

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 (CS) or not clinically significant (NCS). 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 may be documented as adverse events, depending on the interpretation of the Investigator (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.

The Investigator will receive Sponsor defined alerts from the central lab. The Investigator will review the lab alerts and assess clinical significance for potential adverse events.

Blood samples for biomarker, exploratory research, and Pharmacokinetic (PK) analysis will be collected and processed as indicated in Section 5.3.1.2 and Section 5.3.2 (PK). Samples will be shipped to the Central Laboratory by the Study Site and then shipped by the Central Laboratory to AbbVie for analysis.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, subject can be rescheduled to return within 30 days to have blood drawn.

Study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there are no safety concerns for the subject to continue use of the study drug in the absence of current labs. If the Investigator has any concerns the TA MD should be contacted.

Lipid Panel

The lipid panel consists of LDL cholesterol, HDL cholesterol, triglycerides and total cholesterol; and should be obtained in the morning following an overnight fast (minimum of 8 hours); however, there may be circumstances when the sample is obtained later in the day and/or not under fasting conditions. If the sample was obtained with 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.

Serology Testing for Hepatitis and HIV

Subjects will be tested for HAV-IgM, HBsAg, HCV Ab, HIV and 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 and anti-HIV Ab testing will be retained confidentially by the study site.

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.

Endocrine Panel

The endocrine panel consists of the following analytes: FSH and reflexive TSH.

Pregnancy Testing

Urine pregnancy tests will be performed as outlined 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 the SIS and endometrial biopsy procedures, the subject must have a confirmed and documented negative urine pregnancy test within 24 hours of the procedure(s). In addition, during the Treatment Period, the urine pregnancy test must be negative prior to providing subjects with their next supply of study drug, (including an unscheduled visit at which study drug is dispensed).

Home urine pregnancy test kits will be provided to subjects during the Treatment Period for use at home when subjects are not required to come to the site (e.g., phone contact visits and prior to certain study procedures). Subjects will self-administer the tests and report the result to the site during phone visits or within 24 hours prior to undergoing certain study procedures. Subjects reported test results will be entered in 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 (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 of a pregnancy to the Sponsor and the required follow-up on the subject's fetus, pregnancy and infant outcomes.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that a subject or study personnel cannot come to the site for a study visit requiring a urine pregnancy test because of the COVID-19 pandemic, home pregnancy test kits may be provided to subjects to self-administer at home and report results to study site over the phone. Sites should document the results in source. If a urine pregnancy test cannot be completed, the site will need to reach out to the TA MD to determine further action and if study drug should be discontinued.

Sanitary Product Collection for Alkaline Hematin Assay

Quantitative measurement of the volume of MBL will be performed using the alkaline hematin method. Menstrual blood loss will be assessed in all subjects using validated sanitary products, also referred to as "validated" products. Validated products have undergone analytical testing by the analytical lab to confirm adequate precision and accuracy of blood recovery as well as no or limited interference with the alkaline hematin method.

Subjects will start to collect their sanitary products in the Screening Period over the course of 2 to 3 menstrual cycles to determine eligibility for randomization based on MBL.

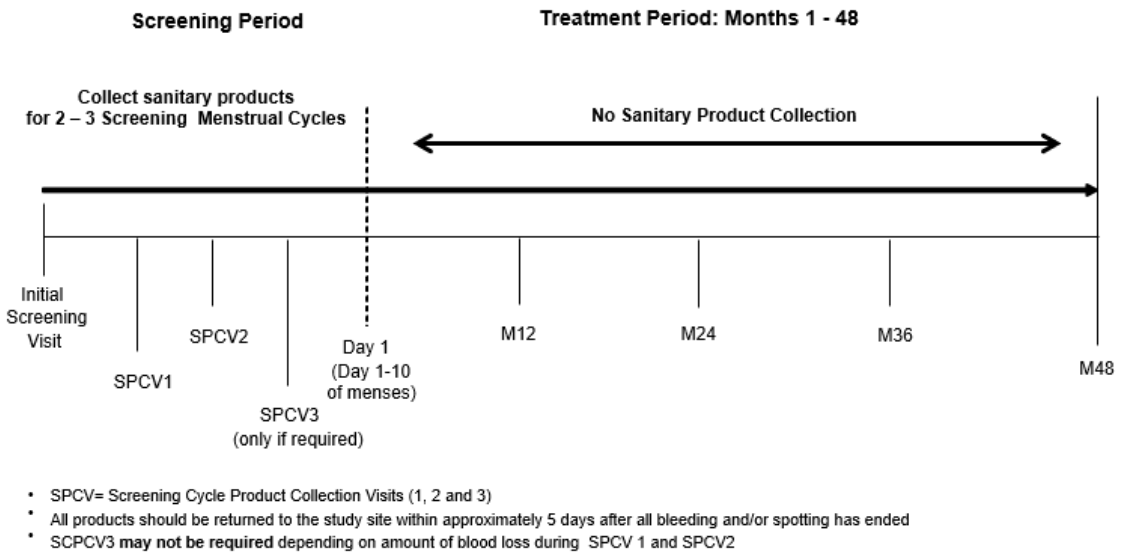
Starting in Screening, subjects will be dispensed sanitary collection kits that consist of validated sanitary products, product collection bags and a keg with screw-on lid for storage as provided by the vendor. It is important that only the sanitary products provided by the Sponsor are used during the study. Validated sanitary products may include:

- Tampax tampons (Regular, Super or Super-Plus absorbency)
- Stayfree Maxi Pads (Regular, Super Long or Overnight absorbency)
- Carefree Original Long Unscented pantiliners

Subjects will be required to collect and retain all sanitary products on days with menstrual bleeding or spotting **(subjects must be instructed to collect and return all used or worn products even if there is no visible blood on the products or if non-validated products were used)** as described in the Alkaline Hematin Laboratory Manual.

The dispensation and collection requirements in the Screening Period is outlined in Figure 3.

Figure 3. Sanitary Product Dispensation and Collection



Screening Product Collection Visits

Subjects will be dispensed a product collection kit and will collect sanitary products on days with bleeding or spotting. Subjects will visit the site within approximately 5 days after cessation of bleeding or spotting for Screening Menstrual Cycles 1 and 2, and if applicable, Screening Menstrual Cycle 3 Product Collection Visits. At each Screening Product Collection Visit, sanitary products to measure MBL will be collected and a venous blood sample will be obtained. The site will submit the sanitary products and venous blood sample to the Alkaline Hematin Laboratory for analysis of MBL volume to determine eligibility. To be eligible for the study based on MBL, a subject must demonstrate > 80 mL for each of 2 menses in Screening. Subjects will continue to collect sanitary products in screening until the results confirm a second eligible menstrual cycle has been met.

Additional screening menstrual cycles may be permitted; however the situation must be discussed with AbbVie prior to allowing additional product collections. Screening Menstrual Cycle 1 for menstrual bleeding assessment begins with the first day of bleeding or spotting associated with menses.

If a subject has a known history of HMB and her first screening MBL amount is ≤ 80 mL due to a variety of factors that may include but is not limited to the following:

- missed collection of products,
- submission of non-validated products (products that have not been tested to determine the level of interference with the alkaline hematin assay), or
- an atypical menstrual cycle, or
- if a subject misses the collection of sanitary products for one of the screening menstrual cycles

The Study Site must consult with AbbVie for further instructions, which may include the collection of sanitary products for an additional menstrual cycle. The subject may still be

eligible for randomization if she demonstrates blood loss > 80 mL during at least 2 screening menstrual cycles. Table 5 provides an overview of eligibility based on MBL.

Table 5. Menstrual Blood Loss Volume Eligibility

Screening Cycle 1 Blood Loss	Screening Cycle 2 Blood Loss	Screening Cycle 3# Blood Loss	Eligible
> 80 mL	> 80 mL	Not needed	Yes
> 80 mL	≤ 80 mL	> 80 mL	Yes
≤ 80 mL*	> 80 mL	> 80 mL	Yes

There may be instances when a 4th cycle needs to be collected due to certain circumstances. Study Site must also consult AbbVie for approval in the event a 4th cycle is needed to determine eligibility based on MBL.

* If Screening Cycle 1 blood loss is ≤ 60 mL, study site must consult AbbVie for approval to collect sanitary products for additional menstrual cycles in screening. Subjects with a Screening Cycle 1 blood loss between 60 and 80 mL may collect Screening Cycle 2 to determine eligibility.

Sites will contact the Interactive Response Technology (IRT) to register the date of the visit for the first subject who completes the Screening Cycle 2 Product Collection Visit. The registration of this visit will trigger the initial shipment of study drug to the study site.

Return of Sanitary Products to Alkaline Hematin Laboratory

The site will submit the sanitary products and applicable venous blood sample collected during the screening period to the Alkaline Hematin Laboratory for analysis as outlined in the Alkaline Hematin Laboratory Manual.

Use of Non-Validated Products

All subjects are required to only use validated products provided by the Sponsor, however in cases when a subject used non-validated products (a product not provided for use in the study), the subject should be instructed to collect and submit the non-validated products to the site. Site staff is to ensure subject is re-educated on the use of validated products and should be source documented.

Electronic Questionnaires and Quality of Life Assessments

Prior to the start of the study, detailed instructions and training for study site staff administering these 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, Study Activities, 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 directly into the electronic device provided to site.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that a subject or study personnel cannot come to the site because of the COVID-19 pandemic, subject visits may be conducted via phone or video conference. The C-SSRS, UFS-QoL and PGIC-MB may be administered by site staff over the phone or video conference. In this situation, sites will read the PRO questions and response options to the subject, record the subject's responses on paper (source), and transcribe into the electronic device provided to the site. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by video conference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded in the source along with who collected the information.

Reason for Study Participation

In order to better understand the reason why a study participant has decided to enroll in this study, subjects will complete the single-question Reason for Study Participation Questionnaire at the Day 1 Visit.

Physician Surgery Questionnaire

Each physician will be asked to complete the Physician Surgery Questionnaire (PSQ) to evaluate the likelihood that the Physician would consider surgery or a surgical procedure as one of the treatment options related to uterine fibroids for the subject.

Uterine Fibroid Symptoms Quality of Life (UFS-QoL) (4-Week Recall)

The UFS-QoL is a disease-specific self-administered questionnaire used to measure health-related quality of life in women with symptomatic uterine fibroids. Each subject will be asked to complete a UFS-QoL Questionnaire[8] using 4-week recall to report fibroid-related symptoms experienced during the previous 4 weeks.

Patient Global Impression of Change – Menstrual Bleeding (PGIC-MB)

Subjects will use the PGIC-MB to assess the change in their severity of menstrual bleeding (from very much improved to very much worse) since initiation of study drug by choosing one of seven responses.

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/Since Last Visit C-SSRS questionnaire will be administered by the site staff using the electronic tablet at the time points specified in Appendix C.

During Screening or at the Day 1 visit, prior to randomization, any subject noted to have suicidal ideation with plan 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. If the subject expresses suicidal ideation on the C-SSRS

or via clinical interview at any time during the study, the Investigator should take appropriate action and then 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 will be administered by site staff at the time points outlined in Appendix C. The C-SSRS administered at the Day 1 Visit will serve as the baseline for clinical assessment.

Return to Menses

Subjects will be asked about return to menses using the Return to Menses Questionnaire in the Post-Treatment Follow-Up Period, as outlined in the Study Activities, Appendix C. Site staff will ask subjects if they have had a menstrual period since discontinuation of study drug and record subjects' responses on the site tablet. If the subject indicates she has not returned to full menses, site staff will continue assess menstruation and repeat the questionnaire at subsequent post-treatment follow-up visits, as applicable. The date when full menses returned will be documented in the source documents and eCRFs.

Randomization and Assignment of Subject Numbers

The site will contact 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 will be assigned. The same subject number will be used to identify the subject throughout the Screening, Treatment and Post-Treatment Follow-Up Periods. In Screening, the site will contact IRT at the Screening Cycle 2 Product Collection Visit to register the date of the visit for the first subject who completes the Screening Cycle 2 Product Collection Visit. The registration of this visit will trigger shipment of clinical drug supplies to the study site. If the subject is not randomized into the study, the reason for screen failure will be documented in the eCRF and the site will register the subject as a screen failure in IRT.

At the Day 1 Visit, eligible subjects will be randomized to 1 of 2 treatment groups by using IRT and providing the subject number the subject received during Screening or

Washout. During the randomization contact session, a unique randomization number and study drug kit numbers will be assigned by the IRT according to a randomization schedule generated by the Statistics department at AbbVie.

During the Treatment Period, sites will register each on-site visit in IRT in order to obtain the appropriate amount of scheduled re-supply of study drug to dispense to each subject. In the event study drug becomes lost or damaged, the site can contact IRT to obtain an unscheduled re-supply of study drug kit numbers 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 Post-Treatment Follow-Up Period.

5.3.1.2 Collection and Handling of Biomarker and Optional Exploratory Research Samples

Samples for biomarker and optional exploratory research will be collected. 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.

All research samples should be collected, labeled, and shipped as outlined in the study specific lab manual. AbbVie (or people or companies working with AbbVie) will store the 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 uterine fibroids and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

Biomarker Blood Samples for Estradiol (E2) Assay

A single blood sample will be collected at each time point indicated in Appendix C to be used for the analysis of E2. The blood samples for assay of estradiol will be collected in one 6 mL evacuated collection tube without anticoagulant (red cap, no gel separators to be

used). Sufficient blood volume will be collected to provide approximately 3 mL serum from each sample.

On Day 1, estradiol samples will be collected prior to dose. The date and time of collection will be recorded on the Central Laboratory Requisition Form. Samples collected at all visits other than Day 1 will be drawn at any time during the visit.

Samples for Pharmacogenetic Exploratory Research (Optional)

Optional whole blood samples for DNA (Deoxyribonucleic acid) and RNA (Ribonucleic acid) isolation will be collected on Day 1, Month 12 and Premature Discontinuation Visit (if applicable) from each subject who consents to provide samples for exploratory research.

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, also known as PK samples, will be collected by venipuncture into 4 mL evacuated K_2-ethylenediaminetetraacetic acid (K_2EDTA)-containing collection tubes at the time points indicated in Appendix C, Study Activities. 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 on the Central Laboratory 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 Drug Analysis Department at AbbVie. Plasma or serum concentrations of other possible metabolites may be determined with validated or non-validated methods.

5.3.3 Efficacy Variables

The objective of this study is to evaluate the long term safety and tolerability of elagolix 300 mg BID with E2/NETA, and as such, no primary efficacy endpoint is defined.

5.3.3.1 Questionnaires and Quality of Life Variables

- UFS-QoL Questionnaire
- Physician Surgery Questionnaire
- Patient Global Impression of Change (PGIC)-MB Questionnaire
- Reason for Study Participation Questionnaire

5.3.4 Safety Variables

- Change from baseline in BMD measured by DXA
- Number and percentage of subjects reporting treatment-emergent adverse events (TEAEs)
- Number and percentage of subjects reporting adverse events of special interest (AESI)
- Change from baseline in clinical laboratory parameters
- Change from baseline in vital signs
- Endometrial biopsy and pelvic ultrasound findings
- Columbia Suicide Severity Rating Scale (C-SSRS)

5.3.5 Pharmacokinetic Variables

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

5.3.6 Biomarker and Exploratory Research Variables

The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids, metabolites or hormone levels (E2). The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to Elagolix (or drugs of the same or similar class) or the development and progression of uterine fibroids 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. Each subject will be withdrawn from 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 requires surgical intervention for treatment of uterine fibroids and menstrual bleeding or other procedures including hysterectomy, myomectomy, uterine artery embolization, high intensity focused ultrasound (HIFU), endometrial ablation, dilation and curettage (D&C), etc. during the Treatment Period. In the Post-Treatment Follow-Up Period these procedures do not

warrant withdrawal if performed during the Post-Treatment Follow-Up Period unless a hysterectomy with bilateral salpingo-oophorectomy (BSO) is performed in the Post-Treatment Follow-Up Period and the subject does not plan to use Hormone Replacement Therapy within 1 month of the surgery date.

- The subject becomes pregnant or has a positive serum pregnancy test.
- The subject has SGPT/ALAT or SGOT/ASAT elevation > 5 times the upper limit of normal, confirmed upon repeat testing during the Treatment Period.
- The subject develops clinically significant gynecological findings or condition on either the TAU/TVU (confirmed by repeat TAU/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 T-score < –2.5 in the lumbar spine, total hip or femoral neck, a BMD decrease 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 requires use of prohibited medications to manage or treat bone mineral density changes during the Treatment Period as described in Section 5.2.3.5. Subject continuation in the Post-Treatment Follow-Up Period is at the discretion of the AbbVie TA MD.
- Heavy menstrual bleeding during the Treatment Period that requires a blood transfusion at any time after having taken 28 days of study drug.
- In the Investigator's opinion, the subject is unable or unwilling to comply with study-related assessments and procedures.
- 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 of last dose of study drug, if possible) and undergo

study procedures as outlined in Appendix C. Subjects who prematurely discontinue during the Treatment Period are expected to enter the Post Treatment Follow-Up Period for up to 12 months unless discontinuation is due to pregnancy.

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 in source and in the eCRFs.

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 6.1.6 for instructions on reporting of a pregnancy to the Sponsor and the required follow-up on the subject/fetus and live births.

Subjects who prematurely discontinue will have a DXA scan performed at the Premature Discontinuation Visit:

- 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, unless a DXA scan has been performed within the prior 3 months of Premature Discontinuation.

Subjects who prematurely discontinue from treatment and enter Post-Treatment Follow Up Period and have had a TAU/TVU and DXA within the prior 3 months will not be required to repeat these procedures at the Premature Discontinuation Visit.

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.

Upon discontinuation from the Treatment Period, all used, unused and unopened study drug containers will 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 in writing 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.

5.4.3 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 treatment or prevents a subject from taking study drug

- Due to malfunction of barrier 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).

Additionally, there may be times when a subject has had treatment interruption due to having forgotten to take study medication, lost study medication, etc. If the subject has missed 10 or more consecutive days of dosing (with either elagolix/E2/NETA or Placebo), the AbbVie TA MD must be consulted to determine whether the subject may resume study drug administration or continue in the Treatment Period.

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects will be randomly assigned by IRT to receive one of the following treatment groups for a total of up to 48 months of treatment:

- elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) (n = 335) for 48 months
- placebo (n = 165) for the first 12 months, then switch to elagolix 300 mg BID plus E2/NETA QD for the remaining 36 months

Safety of using elagolix (300 mg BID) in combination with estradiol 1.0 mg/norethindrone acetate 0.5 mg has already been evaluated in clinical studies of 6-month duration as discussed earlier in Section 3.2.3.

The treatment administration is presented in Table 6.

Table 6. Treatments Administered

		Investigational Product			
Treatment Group	**Dosing Time**	**Elagolix 300 mg Tablets**	**Elagolix Placebo Tablets**	**E2/NETA Capsules**	**Matching E2/NETA Placebo Capsules**
Placebo	AM	0	1	0	1
	PM	0	1	0	0
Elagolix 300 mg BID plus E2/NETA QD	AM	1	0	1	0
	PM	1	0	0	0

A 3-month supply of each study drug plus extra medication will be dispensed beginning at Day 1 throughout the treatment period.

Year 1 Treatment Period

The elagolix study drug, consisting of elagolix or matching placebo, 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 dose (morning dose) and first E2/NETA dose of study drug at the study site on Day 1 (Randomization) whether the subjects visit is scheduled in the morning or afternoon. Subjects will be instructed to self-administer their study drug throughout the 12-month Treatment Period.

Year 2, 3 and 4 (Open-Label) Treatment Period

Study drug treatment after Treatment Month 12 will be open-label in which study drug will be dispensed every 3 months (during the on-site visits). The elagolix study drug will be supplied in a carton and the E2/NETA study drug will be supplied in a separate carton.

Study drug will be taken orally twice daily for the entire 48-month Treatment Period. A morning dose of 1 tablet (elagolix or placebo) and 1 capsule (E2/NETA or placebo) and an evening dose of 1 tablet (elagolix or placebo) should be taken each day approximately 12 hours apart. Study drug should be taken with approximately 8 oz. (240 mL) of water

without regard to food. Study drug should be taken at approximately the same time each morning and evening to promote compliance.

If the subject forgets to take the morning dose, 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 will 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 scheduled visit.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Depending on the local regulations, provisioning of study drug for direct-to-patient (DTP) and direct-from‑patient (DFP) transfer because of the COVID-19 pandemic will be available per request. AbbVie should be notified.

Sites can utilize Marken and/or another local courier for drug shipment in such circumstances. Shipments may also include other study supplies (e.g., pregnancy tests, paper copies of PROs). AbbVie has set up an agreement with Marken (third-party vendor) for sites to use to ship study drug to (and from as applicable) subjects. Shipments of study drugs from the study site to a subject's home will be appropriately temperature-controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

- Sites will be responsible for meeting IRB reporting requirements and submitting the booking form to the local IRB (as applicable).

The investigator must discuss the DTP/DFP process with the subject:

- Obtain consent to provide delivery information to Marken and/or local courier and document this in the source.
- Obtain results of required safety procedures (e.g., urine pregnancy testing) before registering subject dispensation of study drug in IRT.
- Confirm that the subject will be available to accept delivery.
- The site will follow up with the subject after shipment is received.
- The subject should maintain the drug containers, as well as any unused drug for return to site.

Sites will be required to retain documentation of the shipment for the IP accountability and monitoring. AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

5.5.2 Identity of Investigational Product(s)

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

Table 7. Identity of Investigational Products

Study Drug	Formulation	Route of Administration	Manufacturer
Elagolix	Film-coated 300 mg tablets	Oral	AbbVie
Matching Elagolix Placebo	Film-coated Placebo tablets	Oral	AbbVie
E2/NETA	Estradiol 1.0 mg/Norethindrone acetate 0.5 mg tablet	Oral	Pharmaceutics International, Inc Or Novo Nordisk Or Amneal Pharmaceuticals
E2/NETA*	Estradiol 1.0 mg/Norethindrone acetate 0.5 mg capsules*	Oral	Commercial Tablets: Pharmaceutics International, Inc Or Novo Nordisk Or Amneal Pharmaceuticals
Matching E2/NETA Placebo	Placebo capsules	Oral	AbbVie

* Commercially-available E2/NETA tablets are over-encapsulated to maintain study blinding.

5.5.2.1 Packaging and Labeling

AbbVie will supply blinded study drug in monthly kits (i.e., cartons) for the 12-month Treatment Period using compliance packaging. Study drug is provided at each dispensing visit. The study drug consists of elagolix or matching placebo tablets and the other study drug consists of E2/NETA or matching placebo capsules. Each kit contains 5 blister cards, with each blister card containing 7 days of study medication. There are 4 weekly blister cards and 1 extra medication blister card in each kit to supply enough medication for 4 weeks (28 days) of dosing, plus an extra week's supply.

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

AbbVie will supply open-label study drug in 3-monthly kits (i.e., cartons) for the Year 2, 3 and 4 Treatment Period which will not include the compliance packaging. Two kits of study drug will be provided at each dispensing visit. One kit consists of elagolix tablets and the other kit consists of E2/NETA tablets. The elagolix kit contains 12 weekly blister cards and 1 extra medication blister card for a total of 13 blister cards. Each individual elagolix blister card contains 14 tablets for a 7-day (weekly) supply study medication.

The E2/NETA kit contains 3-monthly blister cards or dial packs and 1 extra blister card or dial pack, with each blister card or dial pack containing 28 days 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.

The study medication is 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(s)

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 open label E2/NETA blister card or dial pack must be stored in the outer carton for protection from light.

The study medication storage temperature must be recorded each business day. Temperature excursion must be entered into AbbVie Temperature Excursion Management

System (ATEMS) immediately by the site staff and study drug should not be dispensed until ATEMS or AbbVie deems the drug as acceptable.

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 the 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 receive one of the treatment groups as outlined in Section 5.5.1 upon entry into the 12-month Treatment Period. At the Year 1 Treatment Month 12, all subjects will be re-assigned by IRT to receive open label elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD), including subjects previously randomized to placebo. Subjects re-assigned by IRT will not be assigned new subject numbers.

Study drug must not be dispensed without contacting IRT. Study drug may only be dispensed to subjects enrolled in the study according to kit numbers provided by the IRT.

The randomization schedule will be computer generated by the Statistics Department at AbbVie, North Chicago, IL prior to the start of the study. A copy of all of the randomization schedules will be kept by the Statistics Department at AbbVie and a copy will be forwarded to the IRT provider.

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 to one of the two treatment groups as described in Section 5.5.1.

Study drug will be initiated at the study site on Day 1 (Randomization). Subjects will be instructed to 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 (used, unused or unopened) at the subsequent on-site visit.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

Each 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 staff and subject will remain blinded to each subject's double-blind treatment assignment 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 of 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 (used/unused/unopened) to the study site staff at study visits throughout the Treatment Period or Premature Discontinuation visit (if applicable).

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.

During 12-month Treatment Period, daily recordings of study drug dosing will be obtained using a compliance packaging blister card for all subjects (for both elagolix/E2/NETA and matching placebo).

During the Treatment Period, on-site or phone visit or Premature Discontinuation visit, the subject will be asked to confirm whether doses were taken and to provide the dates and approximate times of the last 4 scheduled doses prior to the study visit. The subject reported data will be recorded in source and in the eCRF.

Sites should instruct subjects not to remove extra or multiple medications 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 subject has removed a number of extra medications, 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.

Compliance packaging will be used in the 12-month Treatment Period only and data collected from kit scanning will be used for exposure response analyses.

During the Treatment Period, the site staff will review study drug compliance with subjects either during an on-site or phone visits. During the phone visits, subjects will be asked if they are taking the study drug as indicated and information will be documented in source.

During on-site visits any discrepancies in the number of tablets/capsules to be taken and the number of tablets/capsules returned do not add up to the number of tablets/capsules dispensed, an explanation and appropriate information, including re-training if provided, should be recorded in the source documents.

If a subject missed more than 10 consecutive days of taking study drug, the AbbVie TA SD should be notified to determine whether the subject may continue.

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 will also include the lot number, kit number, CSSR number, the number of blister cards/cartons dispensed, initials of person who dispensed the drug, and the date study drug was dispensed for each subject. In addition to using IRT inventory, an accurate inventory of study drug can 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 used, unused and unopened 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that a subject cannot come to the site because of the COVID-19 pandemic, the site may contact the IRT for kit assignment after ensuring subject is eligible to continue with study drug dosing and confirming that a home urine pregnancy test was performed and the result was negative. Study drug dispensing can then be undertaken as outlined in Section 5.5.1.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This Phase 3b study will be conducted as a randomized, sequential, 12-month double-blind placebo-controlled, 36-month open-label, multi-center study in premenopausal women 18 to 50 years of age with HMB associated with uterine fibroids.

This study will evaluate the long-term safety of elagolix 300 mg BID plus E2/NETA in subjects with HMB associated with uterine fibroids. The study will also assess the impact of elagolix 300 mg BID plus E2/NETA on BMD in women with HMB associated with uterine fibroids after up to 48 months of treatment.

5.6.2 Appropriateness of Measurements

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.

Regarding efficacy measures, HMB is the most common symptom of women with uterine fibroids. The quantitation of menstrual blood loss using the alkaline hematin method on sanitary products has been validated by the analytical testing laboratory. Pelvic

ultrasound and SIS are standard methods for assessing uterine fibroid size, fibroid and uterine volume. Endometrial biopsy is a standard method for assessing endometrial safety. DXA is the established gold standard method to assess changes in BMD.

5.6.3 Suitability of Subject Population

Premenopausal women 18 to 50 years of age with HMB (> 80 mL per menstrual cycle) and uterine fibroids were selected for this study because that is the population who suffer from HMB associated with uterine fibroids. The lower bound of the age limit (18) was chosen based on the relative paucity of adolescent females with symptomatic uterine fibroids prior to age 18, and the upper age of 50 is included to reduce the risk of subjects becoming menopausal during the study. No studies in females outside of the reproductive years are necessary for this proposed indication.

5.6.4 Selection of Doses in the Study

The results of the 3-month Phase 2a dose finding, Proof-of-Concept (POC) study indicate that elagolix 300 mg BID was the most effective dose in reducing HMB associated with uterine fibroids. The 6-month Phase 2b safety/efficacy study confirmed these results and also demonstrated that E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) was effective in preventing BMD loss and ameliorating vasomotor symptoms due to estrogen suppression. The data (PK/PD) from the multiple ascending dose (MAD) and folliculogenesis studies in healthy subjects also provide additional support for the targeted elagolix dose. All of these studies have demonstrated an acceptable safety and tolerability profile.

Based on the totality of safety and efficacy data, elagolix 300 mg BID with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD) was selected for further evaluation in Phase 3. The maximum elagolix dose administered in this study will not exceed a total daily dose of 600 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 Section 6.1 through Section 6.1.6. For product complaints, please refer to Section 6.2.

All adverse events will be followed to a satisfactory conclusion.

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 staff, or reported spontaneously by the subject will be recorded.

All adverse events will 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. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities 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.

A BMD decrease at any anatomic location (lumber spine, total hip or femoral neck) during the Treatment Period that leads to discontinuation from study drug should be reported as an adverse event.

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

For some adverse events, such as SAEs and adverse events of special interest (AESI), such as elevated liver transaminases, bone mineral density decrease/fractures, and mood and depression-related events, hot flashes and other non-bone hypoestrogenic events, lipid abnormalities, cardiovascular events, thromboembolic events, hormonally sensitive malignancies, and alopecia, AbbVie may require additional information, including family history, to be collected and recorded in the eCRF.

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.

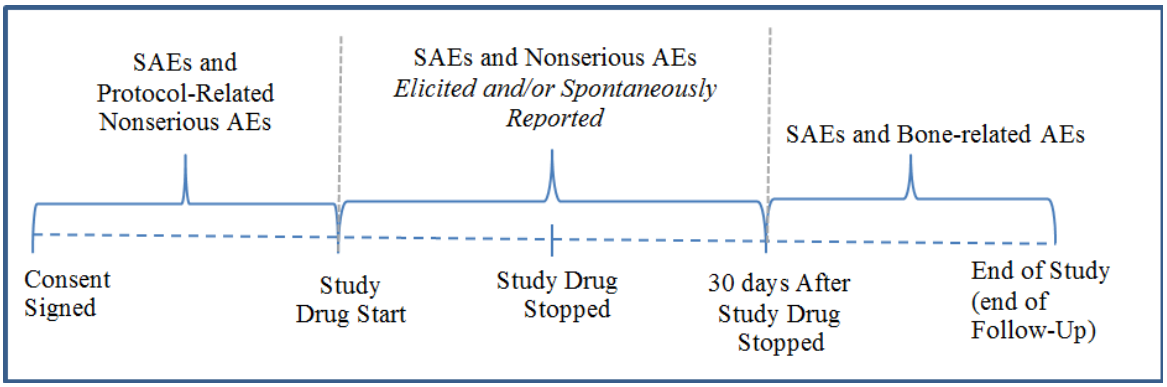
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an Other cause of event must be provided by the Investigator for the serious adverse event.

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 Post-Treatment 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 4.

Figure 4. 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: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

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

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

Men's and Women's Health Safety Line
Phone: (847) 935-7577
Fax: (847) 785-8247
Email: GPRD_SafetyManagement_Hormones@abbvie.com

For any subject safety concerns, please contact the physician listed below:

[redacted] MD, Ph.D.
[redacted]
Specialty Development
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Phone:
Mobile:
Email: [redacted]

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: +1 (973) 784-6402

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed:

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

  If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the Investigator should contact the Sponsor emergency medical contact listed above before reintroducing study drug.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the Treatment or Post-Treatment 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 after receiving at least one dose of study drug through 30 days following the last dose of study drug. 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 Post-Treatment 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 the pregnancy 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, any 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.

For each subject with a confirmed pregnancy, the Investigator will provide information about the option to participate in an elagolix pregnancy registry (P18-954) for pregnancy outcomes. The contact information for the Bloom Pregnancy Registry is in the Oriahnn/Orilissa label (pregnancy registry telephone number: 1-833-782-7241).

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,

including those that may be due to the COVID-19 pandemic), 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] Pharm D, PhD
Specialty Development
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Phone:
Mobile:
Email: [redacted]

Alternate Contact:

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

Phone:
Mobile:
Email: [redacted]

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

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP).

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 0.050 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.

In general, data will be summarized for the 12-month placebo-controlled double-blind Treatment Period, the open-label Treatment Period, and the Post-Treatment Follow-Up Period separately.

In the 12-month placebo-controlled double-blind Treatment Period, data will be summarized by treatment group (the elagolix 300 mg BID plus E2/NETA group and the placebo group). Comparisons of safety will be made between the elagolix 300 mg BID plus E2/NETA group and the placebo group in the 12-month Treatment Period.

In the open-label Treatment Period, summaries will be provided for each of the following treatment groups of subjects.

1. Subjects randomized to elagolix 300 mg BID plus E2/NETA in the 12-month Treatment Period and continued to receive elagolix 300 mg BID plus E2/NETA in the open-label Treatment Period;
2. Subjects randomized to placebo in the 12-month Treatment Period, and switched to elagolix 300 mg BID plus E2/NETA in the Open-label Treatment Period.

Statistical tests will only be made in the double-blind Treatment Period. No statistical tests will be made in the Open-label Treatment Period and the Post-Treatment Follow-Up Period.

8.1.2 Data Sets Analyzed

Full Analysis Set

The full analysis set which is comprised of all randomized subjects who took at least one dose of the study drug will be used for all efficacy analyses and baseline analyses unless otherwise specified in the Statistical Analysis Plan (SAP). The data from the full analysis set will be presented by the treatment group assigned at the time of randomization.

Safety Analysis Set

The safety analysis set includes all randomized subjects who took at least one dose of the study drug. Subjects will be analyzed according to the treatment they actually received, defined as the randomized treatment if the patient took at least one dose of that treatment during the 12-month placebo-controlled double-blind Treatment Period, or the first treatment received if the randomized treatment was never received during the 12-month placebo-controlled double-blind Treatment Period. All safety analyses will be performed based on the safety analysis set unless otherwise specified in the SAP.

The All Elagolix plus E2/NETA Analysis Set is defined as subjects who received at least 1 dose of elagolix plus E2/NETA in the study (either in the placebo-controlled or open-label Treatment Periods). Subjects will be summarized based on the actual treatment received at the time of randomization (elagolix plus E2/NETA or placebo).

8.1.3 End of 12-Month Placebo-Controlled Treatment Period Analysis

An end-of-placebo-controlled treatment period analysis 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 Treatment Periods) and the Follow-Up Period up to the data cut-off for the interim lock. 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 for the comparison between treatment and placebo group at 12 months of safety and efficacy endpoints, no additional adjustment of alpha-level is necessary.

8.1.4 Treatment Month 24, Month 36, Month 48 and Other Timepoints Analyses

At the end of Treatment Month 24, Month 36, Month 48 or other timepoints during the open-label period, analysis of the safety and efficacy safety variables may be performed

after the last subject completes the Treatment Month 24, Month 36, Month 48 visit or other timepoint during the open-label period, 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.

8.1.5 Demographic, Baseline Characteristics and Concomitant Medications

Demographic and baseline characteristics will be summarized by treatment group.

Medical history and gynecological medical/surgical history data will be coded using system organ classes (SOCs) and preferred terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA) by treatment group. The duration of the study drug exposure will be summarized by treatment group.

Protocol deviations and reasons for 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 non-missing assessment obtained prior to the initiation of the study drug unless otherwise specified.

8.1.6 Efficacy

8.1.6.1 Primary Efficacy Variable

8.1.6.1.1 Primary Analysis

As the objective of this study is to evaluate the long-term safety and tolerability of elagolix 300 mg BID with E2/NETA, no primary or secondary efficacy endpoint is defined.

8.1.6.2 Other Efficacy Variables

Other assessments during the placebo-controlled double-bind 12-month Treatment Period include the following:

- PGIC for Menstrual Bleeding Symptom;
- Change from baseline for the UFS-QoL.

UFS-QoL

Improvement in quality of life will be assessed on the UFS-QoL Questionnaire (4-week recall). The change from baseline to each scheduled assessment will be calculated and summarized for each of the UFS-QoL subscales (symptom severity, concern, activities, energy/mood, control, self-conscious and sexual function) and the Health Related Quality of Life Questionnaire (HRQoL) total. The change from Baseline to Month 6 and Month 12 during the double-blind Treatment Period will be analyzed using ANCOVA with treatment as the main effect and corresponding Baseline UFS-QoL as a covariate to compare the elagolix dose group to placebo.

PGIC for Menstrual Bleeding (PGIC-MB):

PGIC-MB is to assess the change in subjects' severity of menstrual bleeding. The number and percentage of subjects in each response category based on PGIC-MB will be summarized at Month 3, Month 6, Month 9 and Month 12 by treatment group. The number and percentage of subjects with response of (a) "Very Much Improved" or "Much Improved," and (b) "Otherwise" will be summarized by treatment group in the 12-month Treatment Period. Comparisons will be made using a Miettinen–Nurminen (M-N) test.

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.

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 in the 12-month Treatment Period unless otherwise specified in the SAP.

Categorical data will be summarized with frequencies and percentages by treatment group. Chi-square test or Fisher's exact test (or its generalization to r × c tables) will be used to analyze treatment group differences for qualitative categorical variables in the 12-month Treatment Period unless otherwise specified in the SAP.

Missing safety data will not be imputed.

Analysis details will be specified in the SAP.

8.1.7.2 Adverse Events

Unless otherwise specified, all summaries/analyses involving AEs will only include treatment-emergent adverse events (TEAEs). TEAEs are defined as any AE with an onset or increased severity after the first dose of study drug and no more than 30 days after the last dose date of study drug. AEs where the onset date is the same as the first dose date of study drug are assumed to be treatment-emergent, unless the first dose time of study drug and the AE start time are collected and the AE start time is prior to the first dose time of study drug. If an incomplete onset date was collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the first dose date of study drug).

AEs starting more than 30 days following discontinuation of the study drug will not be included in the summaries of TEAEs.

TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or higher. TEAEs will be summarized using MedDRA system organ classes (SOCs) and preferred terms (PTs) and grouped by treatment group.

For each TEAE summary, the number and percentage of subjects experiencing at least one TEAE will be presented. Subjects reporting more than one TEAE within a SOC will be counted only once for that SOC. Subjects reporting more than one TEAE for a PT will be counted only once for that PT.

When summarizing TEAEs by relationship or severity, if a subject has an event with unknown severity or relationship, then the subject will be counted in the severity/relationship category of "unknown," even if the subject has a second occurrence of the same event with a severity/relationship present. The only exception is if the subject has a second occurrence of the same event with the most extreme severity (i.e., "severe") or a relationship category of "reasonable possibility." In this case, the subject will be counted under these most extreme severity/relationship categories.

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

- Any TEAE
- Any TEAE reasonably possibly related to study drug
- Any TEAE leading to discontinuation of study drug
- Any treatment-emergent serious AE (SAE)
- Any SAE reasonably related to study drug
- Any AESI (e.g., hypoestrogenic adverse events)

8.1.7.3 Analysis of Laboratory Data and Vital Signs

Changes from baseline in laboratory and vital sign parameters will be summarized by treatment group during the Treatment Periods.

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.

Analysis details will be specified in the SAP.

8.1.7.4 Bone Mineral Density

The within-group percent change from baseline to Months 6, 12, 18, 24, 30, 36, 42 and 48 in BMD will be summarized for each treatment group with mean, standard deviation and two-sided 95% confidence interval. The between-group differences in percent change from baseline to Month 6 and Month 12 in BMD will be summarized with mean and standard error. The percent change from baseline to Month 6 and Month 12 in BMD will be compared between the elagolix 300 mg BID plus E2/NETA group and the placebo group using a model based approach. Two-sided 95% confidence intervals will be constructed for the between group differences in percent change from baseline to Month 6 and Month 12 in BMD.

The number and percentage of subjects with categorized percent change from baseline in BMD decrease will be summarized by treatment group during the Treatment Periods.

Analysis details will be specified in the SAP.

8.1.7.5 Endometrial Biopsy

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

8.1.7.6 Pelvic Ultrasound Findings

The number and percentage of subjects with complex ovarian cysts > 3.5 cm, as well as the number and percentage of subjects with simple ovarian cysts > 5 cm will be summarized by treatment group during the Treatment Periods. The change from baseline in endometrial thickness will be summarized for each treatment group during the Treatment Periods.

8.1.7.7 Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be summarized by treatment group according to published scoring guidelines.

8.1.8 Pharmacokinetic/Biomarker Analysis

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 500 subjects will be randomized (2:1) to elagolix 300 mg BID plus E2/NETA (N = 335) and placebo (N = 165).

Based on clinical review, a sample size of 500 was selected to gather long term safety exposure data in approximately 50 subjects completing 48 months of study drug dosing, with approximately 30 subjects receiving 48 months of active drug elagolix 300 mg BID plus E2/NETA 1/0.5 mg QD.

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. During the COVID-19 pandemic, virtual/remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), and shipping investigational product and/or supplies direct to subjects

to ensure continuity of treatment where allowed. Refer to the Study Procedures sections for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed 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.

In the event a subject withdraws consent to participate from the study, stored biomarker and 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 that their samples be withdrawn. Once AbbVie receives the request, remaining samples will be destroyed. If the subject changes her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

An informed consent, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected and analyzed for optional exploratory research. The nature of the testing should be explained and the subject given an opportunity to ask questions.

If the subject does not consent to provide samples for the optional exploratory research, it will not impact their participation in the study.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent must be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

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

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

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the

study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site staff 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, legibility, and acceptability by AbbVie staff (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) system 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 system 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 be entering 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 study. This access will be available for the duration of the study to the site investigator, as well as delegated staff. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO 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 ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The ePRO data will be collected by the following methods:

Diary Based

- The (instrument/scale) 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 of the study site. All data entered on the device will be immediately stored to the device itself and manually/automatically uploaded to a central server administrated by CRF Health. The Investigator and delegated 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.

Tablet Based

- The (instrument/scale) will be collected electronically via a Tablet/Laptop 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. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by CRF Health. The Investigator and delegated 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

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Prior to enrolling any subject in the study, a Site Training Visit will be held with AbbVie staff (and/or their representatives), the investigators, and the appropriate site staff. 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 staff at the study site will be trained on the study procedures, when applicable, by an AbbVie monitor or designee.

The AbbVie monitor or designee will monitor the study site throughout the study. A source document review will be performed against entries on the eCRFs and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. 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, lipid and endocrine panels, urine pregnancy tests, urinalysis, Pap smears 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 staff from AbbVie.

Alkaline hematin analysis will be performed by Alkaline Hematin Laboratory. The data from these analyses will be electronically transferred from the Alkaline Hematin Laboratory to the study database.

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

Pelvic ultrasound, SIS and MRI (if applicable) scans 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 DXA Reader. The results of these scans will be electronically transferred from the Central DXA Reader to the study database.

12.0 Use of Information

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 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.

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.

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 submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory 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.

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 3b Study to Evaluate the Long-Term Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women
Protocol Date:	02 May 2022

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]		Clinical Development
		Clinical Development
		Clinical Operations
		Clinical Pharmacokinetics
		Clinical Development
		Statistics
		Statistics

Appendix C. Study Activities

Procedure	WO (if Applicable) and Screening Period			Year 1 Treatment Period[a]														
	WO Period	SCR Visit	Cyc1e 1 –3‡ PCV[b]	D 1[c]	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	Unsch Visit	PD (If Appl.)
Informed Consent	X	X[&]																
Phone Visit[d]					X	X		X	X		X	X		X	X			
Medical/Social History	X	X[&]		X[e]														
Gynecological/ Obstetrical and Uterine Fibroid History	X	X[&]		X[e]														
Complete Physical Examination; Height (H); Weight (W)	X*	X (H, W)[$]		X*,[e]												X (W)[$]		X (W)[$]
Gynecological (External Genitalia, Pelvic and Breast) Examination		X														X		X
Vital Signs	X	X	X	X[e]			X			X			X			X	X	X
12-Lead Electrocardiogram (ECG)		X																
Mammogram		X[∞]														X[f]		X[g]
Pap Test		X																X[g]
Endometrial Biopsy[h,i]		X														X		X[g]
Pelvic Ultrasound[@]: TAU, TVU	X[j]	X[&]		X[k]												X		X[g]
Saline Infusion Sonohysterography (SIS)[i]		X																
MRI (if applicable)[l]		X																
DXA Scan		X								X						X		X[g]

Procedure	WO (if Applicable) and Screening Period			Year 1 Treatment Period[a]														
	WO Period	SCR Visit	Cyc1e 1 –3‡ PCV[b]	D 1[c]	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12	Unsch Visit	PD (If Appl.)
Dispense Sanitary Products and Collection Kit (Keg, Collection Bags, etc.)		X	X^															
Start Collection of Sanitary Products		X																
Return Sanitary Products; draw venous blood sample			X															
Clinical Safety Labs: Chemistry, Hematology, Lipid Panel and Urinalysis		X		X												X		X
Lipid Panel and Subset of Chemistry Labs: ALT, AST, Bilirubin and Alkaline Phosphatase							X			X			X					
Urine Test for Gonorrhea and Chlamydia (Optional)		X[m]																
Vitamin D Testing		X																
Serology (Hepatitis and HIV Screens)		X																
Endocrine: FSH and Reflexive TSH		X																
Biomarker Sample: Serum Estradiol (E2)				X[e]			X[n]			X[n]			X[n]			X[n]		X[n]
Pharmacokinetic Sample (PK): Elagolix and NETA Plasma Concentration							X[n]			X[n]			X[n]			X[n]		X[n]

Procedure	WO (if Applicable) and Screening Period			Year 1 Treatment Period[a]														
	WO Period	**SCR Visit**	**Cyc1e 1 –3‡ PCV[b]**	**D 1[c]**	**M 1**	**M 2**	**M 3**	**M 4**	**M 5**	**M 6**	**M 7**	**M 8**	**M 9**	**M 10**	**M 11**	**M 12**	**Unsch Visit**	**PD (If Appl.)**
Pharmacogenetic DNA and RNA Sample (PG) (Optional based on Subject consent)				X[n]												X[n]		X[n]
Urine Pregnancy Tests[o,p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception Counseling/Dispense Contraceptives as necessary[q]	X	X	X	X^	X	X	X^	X	X	X^	X	X	X^	X	X	X^		X
Birth Control Attestation				X			X			X			X			X		X
Reason for Study Participation				X[e]														
PSQ				X[e]														
UFS-QoL				X[e]						X						X		X
PGIC-MB							X			X			X			X		X
C-SSRS – Baseline/ Screening		X		X[e]														
C-SSRS – Since Last Visit							X			X			X			X		X
Randomization				X														
Interactive Response Technology (IRT)	X	X	X[#]	X			X			X			X			X		X
Dispense Study Drug				X			X			X			X			X[r]		
Drug Accountability[d]					X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Event Monitoring[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

D = Day; M = Month; SCR Visit = Screening Visit; WO = Washout; PCV = Product Collection Visit; Unsch Visit = Unscheduled Visit; PD = Premature Discontinuation Visit

‡ If the subject does not demonstrate blood loss > 80 mL during either Screening Cycle 1 or 2, she may qualify for a third cycle assessment of blood loss (Table 5). If required, the subject will collect sanitary products for a third menstrual cycle and will visit the site for a Screening Cycle 3 Product Collection Visit.

& If performed during Washout, do not repeat during Screening Period.

* Brief symptom-directed examination.

$ Complete physical examination; including weight (the subject should not wear shoes during weighing).

∞ Only in subjects ≥ 39 years of age at the time of randomization, unless the mammogram was performed within 3 months prior to Screening. Results must be entered in EDC upon receipt.

@ Subjects with a finding of polyp on pelvic ultrasound during the Treatment Period will undergo evaluation per standard of care which may include an SIS.

^ Site should dispense enough sanitary product collection kits during screening only. In addition, sites should also dispense contraceptives to carry subject over to the next on-site visit.

Screening Cycle 2 Product Collection Visit will be registered in IRT **only** for the first subject who completes the Screening Cycle 2 Product Collection Visit to activate drug shipment to the study site.

a. Refer to Table 1 for Visit and Assessment Windows, for allowable visit and assessment-specific windows during the Year 1 Treatment Period.

b. Visit to occur approximately 5 days after cessation of bleeding or spotting.

c. Day 1 (Randomization) Visit to occur between Days 1 – 10 of the first day of menses (first day of menses is the first day with full menstrual flow).

d. Site staff to evaluate subjects compliance with taking study drug per protocol, assess ongoing adverse events, concomitant medications (if applicable), obtain the results of the subject's self-administered urine pregnancy test, and remind subjects of the importance of consistent use of appropriate and effective use of dual non-hormonal contraception.

e. To either be updated or performed or collected prior to study drug administration. Measurements should be assessed consistently throughout the study.

f. A Mammogram will be performed for all subjects who are 39 years of age or older at time of the scheduled study visit.

g. Mammogram, DXA, Pelvic Ultrasound, Pap test, or Endometrial Biopsy not required if subject prematurely discontinues prior to Treatment Month 6, i.e., received < 6 months of study drug. Refer to Section 5.3.1.1, Study Procedures, Bone Mineral Density (DXA scan) for additional details on performing DXA scan at Premature Discontinuation Visit.

h. An endometrial biopsy is not required during the Treatment Period if the TVU findings indicate an endometrial thickness < 4 mm. If the TVU findings indicate an endometrial thickness ≥ 4 mm then the subject must have an endometrial biopsy performed.

i. Subject must have a confirmed negative urine pregnancy test within 24 hours prior to performing the SIS and Endometrial Biopsy.

j. Ultrasound may be performed prior to Washout (after informed consent is signed) to establish the presence of a qualifying fibroid(s) or uterine volume to avoid subjects from undergoing a lengthy washout of hormonal medications unnecessarily.

k. If subject has had a pelvic ultrasound (TAU/TVU) during washout or screening that is > 120 days from the date the procedure was performed, the pelvic ultrasound will need to be repeated on Day 1.

l. Subjects who have SIS images which were unable to fully assess the endometrial cavity after 2 separate SIS attempts have been made may undergo an MRI for further evaluation in Screening (per imaging vendor request only).

m. Optional urine test for gonorrhea or chlamydia should be performed prior to undergoing the endometrial biopsy. Positive test results will be treated outside of the protocol.

n. Biomarker sample (E2), Pharmacokinetic (PK) (elagolix and NETA) and Pharmacogenetic (DNA and RNA) samples can be drawn at any time during the visit.

o. Study drug must not be dispensed if the subject has a positive urine pregnancy test result at any visit during the Treatment Period. A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. For any subject who has a positive serum pregnancy test result, a TVU must be conducted as early as possible in the first trimester in order to assess the gestational age and estimated due date. The site will immediately inform the subject to discontinue study drug and the subject will be discontinued from the study at the point the pregnancy is confirmed.

p. Dispense home urine pregnancy test kits for subjects to self-administer during the Screening Period, prior to SIS and endometrial biopsy procedure, and for the Phone Visits during the Treatment Period.

q. Subjects are required to use two forms of non-hormonal birth control throughout the Treatment Period. In addition, 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.

r. Study drug kits will continue to be dispensed for those subjects continuing into the open–label Treatment Period.

Study Activities – Year 2 Open Label Treatment Period

	Year 2 Treatment Period[a]												Unsch Visit	PD
	M 13	**M 14**	**M 15**	**M 16**	**M 17**	**M 18**	**M 19**	**M 20**	**M 21**	**M 22**	**M 23**	**M 24**		
Phone Visit[b]	X	X		X	X		X	X		X	X			
Pelvic Ultrasound[@]: TVU, TAU												X		X[c]
Endometrial Biopsy[d]												X		X[c]
Pap Test												X		X[c]
Complete Physical Examination: including weight (W)												X (W)*		X (W)*
Gynecological (External Genitalia, Pelvic and Breast) Examination												X		X
Vital Signs			X			X			X			X	X	X
Mammogram[e]												X		X[c]
DXA Scan						X						X		X[c]
Clinical Safety Labs: Chemistry, Hematology, Lipid Panel and Urinalysis												X		X
Lipid Panel and Subset of Chemistry Labs: ALT, AST, Bilirubin and Alkaline Phosphatase			X			X			X					

	Year 2 Treatment Period[a]												Unsch Visit	PD
	M 13	M 14	M 15	M 16	M 17	M 18	M 19	M 20	M 21	M 22	M 23	M 24		
Biomarker Sample: Serum Estradiol (E2)[f]						X						X		X
Pharmacokinetic Sample (PK): Elagolix and NETA Plasma Concentration[f]						X						X		X
Urine Pregnancy Test[g,h]	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception Counseling/Dispense Contraceptives as necessary[i]	X	X	X[j]	X	X	X[j]	X	X	X[j]	X	X	X[j]		X
Birth Control Attestation			X			X			X			X		X
UFS-QoL						X						X		X
C-SSRS – Since Last Visit			X			X			X			X		X
Interactive Response Technology (IRT)			X			X			X			X		X
Dispense Study Drug			X			X			X			X		
Drug Accountability[b]	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Event Monitoring[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

@ Subjects with a finding of polyp on pelvic ultrasound during the Treatment Period will undergo evaluation per standard of care which may include an SIS.

* Complete physical examination; including weight (the subject should not wear shoes during weighing).

a. Refer to Table 1 Visit and Assessment Windows, for allowable visit and assessment-specific windows during the Year 2 Treatment Period.

b. Site staff to evaluate subjects compliance with taking study drug per protocol, assess ongoing adverse events, concomitant medications (if applicable), obtain the results of the subject's self-administered urine pregnancy test, and remind subjects of the importance of consistent use of appropriate and effective use of dual non-hormonal contraception.

c. Premature Discontinuation prior to the time of the Treatment Month 18 does not require a Mammogram, DXA, Pelvic Ultrasound, Pap test, or Endometrial Biopsy, (i.e., received < 6 months of study drug during the Year 2 Treatment Period). Refer to Section 5.3.1.1, Study Procedures, Bone Mineral Density (DXA scan) for additional details on performing DXA scan at Premature Discontinuation Visit.

d. A negative urine pregnancy result should be obtained on the day of the endometrial biopsy, prior to performing the procedure. An endometrial biopsy is not required during the Treatment Period if the TVU findings indicate an endometrial thickness < 4 mm. If the TVU findings indicate an endometrial thickness ≥ 4 mm then the subject must have an endometrial biopsy performed.

e. Mammograms will be performed for all subjects who are 39 years of age or older at time of the scheduled study visit.

f. Biomarker sample (E2), Pharmacokinetic (PK) (elagolix and NETA) samples can be drawn at any time during the visit.

g. Study drug must not be dispensed if the subject has a positive urine pregnancy test result at a visit during the Treatment Period. A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. For any subject who has a positive serum pregnancy test result, a TVU must be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery. The site will immediately inform the subject to discontinue study drug and the subject will be discontinued from the study at the point the pregnancy is confirmed.

h. Home pregnancy test kits will be dispensed at on-site visits and will be self-administered at home by the subject and results will be reported to site.

i. Subjects are required to continue the use of two forms of non-hormonal birth control throughout the Treatment Period. In addition, 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.

j. Site should dispense enough contraceptives to carry subject over to the next on-site visit.

Study Activities – Year 3 Open Label Extension

	Year 3 Open Lab Treatment Period[a]													
	M 25	**M 26**	**M 27**	**M 28**	**M 29**	**M 30**	**M 31**	**M 32**	**M 33**	**M 34**	**M 35**	**M 36**	**Unsch Visit**	**PD**
Phone Visit[b]	X	X		X	X		X	X		X	X			
Pelvic Ultrasound[@]: TVU, TAU												X		X[c]
Endometrial Biopsy[d]												X		X[c]
Pap Test														X[c]
Complete Physical Examination: including weight (W)												X (W)*		X (W)*
Gynecological (External Genitalia, Pelvic and Breast) Examination												X		X
Vital Signs			X			X			X			X	X	X
Mammogram[e]												X		X[c]
DXA Scan						X						X		X[c]
Clinical Safety Labs: Chemistry, Hematology, Lipid Panel and Urinalysis												X		X
Lipid Panel and Subset of Chemistry Labs: ALT, AST, Bilirubin and Alkaline Phosphatase			X			X			X					

	Year 3 Open Lab Treatment Period[a]													
	M 25	**M 26**	**M 27**	**M 28**	**M 29**	**M 30**	**M 31**	**M 32**	**M 33**	**M 34**	**M 35**	**M 36**	**Unsch Visit**	**PD**
Biomarker Sample: Serum Estradiol (E2)[f]						X						X		X
Pharmacokinetic Sample (PK): Elagolix and NETA Plasma Concentration[f]						X						X		X
Urine Pregnancy Test[g,h]	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception Counseling/Dispense Contraceptives as necessary[i]	X	X	X[j]	X	X	X[j]	X	X	X[j]	X	X	X[j]		X
Birth Control Attestation			X			X			X			X		X
UFS-QoL						X						X		X
C-SSRS – Since Last Visit			X			X			X			X		X
Interactive Response Technology (IRT)			X			X			X			X		X
Dispense Study Drug			X			X			X			X		
Drug Accountability[b]	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Event Monitoring[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

@ Subjects with a finding of polyp on pelvic ultrasound during the Treatment Period will undergo evaluation per standard of care which may include an SIS.

* Complete physical examination; including weight (the subject should not wear shoes during weighing).

a. Refer to Table 1 Visit and Assessment Windows, for allowable visit and assessment-specific windows during the Year 3 Treatment Period.

b. Site staff to evaluate subjects compliance with taking study drug per protocol, assess ongoing adverse events, concomitant medications (if applicable), obtain the results of the subject's self-administered urine pregnancy test, and remind subjects of the importance of consistent use of appropriate and effective use of dual non-hormonal contraception.

c. Premature Discontinuation prior to the time of the Treatment Month 30 does not require a Mammogram, DXA, Pelvic Ultrasound, or Pap test (i.e., received < 6 months of study drug during the Year 3 Treatment Period). Endometrial Biopsy is not required if the subject had an endometrial biopsy within the last 6 months. Refer to Section 5.3.1.1, Study Procedures, Endometrial Biopsy, and Bone Mineral Density (DXA scan) for additional details on performing DXA scan at Premature Discontinuation Visit.

d. A negative urine pregnancy result should be obtained on the day of the endometrial biopsy, prior to performing the procedure. Endometrial Biopsy is not required if the subject had an endometrial biopsy within the last 6 months. Refer to Section 5.3.1.1, Study Procedures, Endometrial Biopsy for additional details.

e. A Mammogram will be performed for all subjects who are 39 years of age or older at time of the scheduled study visit.

f. Biomarker sample (E2), Pharmacokinetic (PK) (elagolix and NETA) samples can be drawn at any time during the visit.

g. Study drug must not be dispensed if the subject has a positive urine pregnancy test result at a visit during the Treatment Period. A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. For any subject who has a positive serum pregnancy test result, a TVU must be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery. The site will immediately inform the subject to discontinue study drug and the subject will be discontinued from the study at the point the pregnancy is confirmed.

h. Home pregnancy test kits will be dispensed at on-site visits and will be self-administered at home by the subject and results will be reported to site.

i. Subjects are required to continue the use of two forms of non-hormonal birth control throughout the Treatment Period. In addition, 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.

j. Site should dispense enough contraceptives to carry subject over to the next on-site visit.

Study Activities – Year 4 Open Label Extension

	Year 4 Open Lab Treatment Period[a]													
	M 37	**M 38**	**M 39**	**M 40**	**M 41**	**M 42**	**M 43**	**M 44**	**M 45**	**M 46**	**M 47**	**M 48**	**Unsch Visit**	**PD**
Phone Visit[b]	X	X		X	X		X	X		X	X			
Pelvic Ultrasound[@]: TVU, TAU												X		X[c]
Endometrial Biopsy[d]												X		X[c]
Pap Test												X		X[c]
Complete Physical Examination: including weight (W)												X (W)*		X (W)*
Gynecological (External Genitalia, Pelvic and Breast) Examination												X		X
Vital Signs			X			X			X			X	X	X
Mammogram[e]												X		X[c]
DXA Scan						X						X		X[c]
Clinical Safety Labs: Chemistry, Hematology, Lipid Panel and Urinalysis												X		X
Lipid Panel and Subset of Chemistry Labs: ALT, AST, Bilirubin and Alkaline Phosphatase			X			X			X					

	Year 4 Open Lab Treatment Period[a]													
	M 37	**M 38**	**M 39**	**M 40**	**M 41**	**M 42**	**M 43**	**M 44**	**M 45**	**M 46**	**M 47**	**M 48**	**Unsch Visit**	**PD**
Biomarker Sample: Serum Estradiol (E2)[f]						X						X		X
Pharmacokinetic Sample (PK): Elagolix and NETA Plasma Concentration[f]						X						X		X
Urine Pregnancy Test[g,h]	X	X	X	X	X	X	X	X	X	X	X	X		X
Contraception Counseling/Dispense Contraceptives as necessary[i]	X	X	X[j]	X	X	X[j]	X	X	X[j]	X	X	X[j]		X
Birth Control Attestation			X			X			X			X		X
UFS-QoL						X						X		X
C-SSRS – Since Last Visit			X			X			X			X		X
Interactive Response Technology (IRT)			X			X			X			X		X
Dispense Study Drug			X			X			X					
Drug Accountability[b]	X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Event Monitoring[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X

@ Subjects with a finding of polyp on pelvic ultrasound during the Treatment Period will undergo evaluation per standard of care which may include an SIS.

* Complete physical examination; including weight (the subject should not wear shoes during weighing).

a. Refer to Table 1 Visit and Assessment Windows, for allowable visit and assessment-specific windows during the Year 4 Treatment Period.

b. Site staff to evaluate subjects compliance with taking study drug per protocol, assess ongoing adverse events, concomitant medications (if applicable), obtain the results of the subject's self-administered urine pregnancy test, and remind subjects of the importance of consistent use of appropriate and effective use of dual non-hormonal contraception.

c. Premature Discontinuation prior to the time of the Treatment Month 42 does not require a Mammogram, DXA, Pelvic Ultrasound, or Pap test (i.e., received < 6 months of study drug during the Year 4 Treatment Period). Endometrial Biopsy is not required if the subject had an endometrial biopsy within the last 6 months. Refer to Section 5.3.1.1, Study Procedures, Endometrial Biopsy, and Bone Mineral Density (DXA scan) for additional details on performing DXA scan at Premature Discontinuation Visit.

d. A negative urine pregnancy result should be obtained on the day of the endometrial biopsy, prior to performing the procedure. Endometrial Biopsy is not required if the subject had an endometrial biopsy within the last 6 months. Refer to Section 5.3.1.1, Study Procedures.

e. A Mammogram will be performed for all subjects who are 39 years of age or older at time of the scheduled study visit.

f. Biomarker sample (E2), Pharmacokinetic (PK) (elagolix and NETA) samples can be drawn at any time during the visit.

g. Study drug must not be dispensed if the subject has a positive urine pregnancy test result at a visit during the Treatment Period. A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. For any subject who has a positive serum pregnancy test result, a TVU must be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery. The site will immediately inform the subject to discontinue study drug and the subject will be discontinued from the study at the point the pregnancy is confirmed.

h. Home pregnancy test kits will be dispensed at on-site visits and will be self-administered at home by the subject and results will be reported to site.

i. Subjects are required to continue the use of two forms of non-hormonal birth control throughout the Treatment Period. In addition, 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.

j. Site should dispense enough contraceptives to carry subject over to the next on-site visit.

Study Activities – Post-Treatment Follow-Up Period

	Post-Treatment Follow-Up[a]		
	Month 1	**Month 6**	**Month 12**
On-site Visit	X		
Phone Visit		X	X
Physical Examination	X[b]		
Return to Menses Questionnaire[c]	X	X	
DXA Scan[d]		X	X
Pregnancy Test[e] Urine (u), serum (s)	X (u, s)	X[f] (u)	X[f] (u)
Serum Estradiol (E2) and FSH sample	X		
Lipid Panel and Subset of Chemistry Labs: ALT, AST, Bilirubin and Alkaline Phosphatase	X		
Review Adverse Events	X[g]		
Review Adverse Events of Special Interest (Bone)[h]		X	X
Review Concomitant Medication	X	X	X

a. Refer to Table 1 Visit and Assessment Windows, for allowable visit and assessment-specific windows during the Post-Treatment Follow-Up Period.

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

c. 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.

d. Site staff to contact subjects to ensure Month 6 and 12 DXA scans are scheduled within the visit window (refer to Table 1).

e. 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 Post-Treatment 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 Post-Treatment Follow-Up Period at the point the pregnancy is confirmed.

f. A negative urine pregnancy test must be obtained within 2 days prior to performing the DXA. 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.

g. Any ongoing adverse events at the end of the Treatment Period will be reviewed for resolution during this visit.

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

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