1.0 Title Page

Clinical Study Protocol M12-815

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

Incorporating Amendments 1, 2 and 3

AbbVie Investigational Product:	Elagolix (ABT-620)
Date:	25 September 2017
Development Phase:	3
Study Design:	Phase 3, randomized, double-blind, multicenter, placebo-controlled study evaluating the efficacy, safety and tolerability of elagolix alone and in combination with estradiol/norethindrone acetate for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women 18 to 51 years of age.
Investigators:	Multicenter Trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted]

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	06 November 2015
Amendment 1	01 December 2015
Amendment 2	23 June 2016

The purpose of this Amendment is to:

- Update Section 1.1 Protocol Amendment: Summary of Changes from Appendix Q to Appendix R

  Rationale: *To correct the typographical error*
- Update following Section 1.2 Synopsis, Section 1.3 List of Abbreviations and Definition of Terms, Section 3.2.3 Pregnancy in Elagolix Studies and Section 5.1 Overall Study Design and Plan: Description to add 'approximate' 2.5 to 3.5 month Screening Period

  Rationale: *To accurately note the variability in screening period and maintain consistency across the protocol*
- Update Section 5.3.1.1 Study Procedures, Central Imaging Procedures to:
  - Clarify that the Month 6 endometrial biopsy and imaging procedures need to be performed 15 days prior to the visit to ensure that images or samples are accepted for review by the central vendor.

    Rationale: *To clarify language that procedures need to be performed within the window, however not all results need to be reported by the central vendor to the site for subject eligibility prior to rollover into the extension study.*
  - Clarify that the pelvic ultrasound report at Month 6 is only required for review if the endometrial biopsy cannot be performed or biopsy results are insufficient.

    Rationale: *To clarify the case when the ultrasound report needs to be reviewed at Month 6 prior to rollover into the extension study.*
  - Add that ICL reports will be issued based on Site Operations Manual.

Rationale: *To provide the documentation reference for types of reports that will be issued by central imaging vendor.*

- Update Section 5.3.1.1 Study Procedures, Qualifying Uterine Fibroids to revise from Multiple Small Fibroids to Multiple Fibroids

  Rationale: *To include all multiple fibroids regardless of size.*

- Update Section 5.4 Removal of Subjects from Therapy or Assessment to clarify when in the Study, surgical interventions and elevated liver enzymes constitute study withdrawal.

  Rationale: *Clarify which subjects require withdrawal during treatment and post-treatment follow up period.*

- Update Section 5.4.4 Delays in Rollover into the Extension Study to:
  - Add the '28-day' interval visit required for subjects awaiting eligibility for the extension study

    Rationale: *To clarify the timing of the monthly interval for when the delay in rollover visit should occur.*

  - Remove language to conduct assessments and procedures in Table 6

    Rationale: *To reflect the update that the procedures are performed at the 28 day interval.*

  - Clarify for subjects not entering the extension study that the next visit in the Post-Treatment Follow-up Period will be a Site Visit and not a Phone Visit

    Rationale: *To correct the error in Amendment 2 which described the Post-Treatment Follow-up Month 1 Visit as a Phone Visit.*

- Update Appendix C Study Activities – Washout, Screening and Treatment Periods and Post-Treatment Follow-Up Period to add footnotes for Endometrial Biopsy Pelvic Ultrasound, MRI and DXA at Month 6

  Rationale: *Clarify which results need to be reported prior to rollover into the extension study.*

- Update Appendix D BI-RADS Classification

  Rationale: *Updating classifications to align with the American College of Radiology BI-RADS Atlas Fifth Edition.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M12-815
Name of Study Drug: Elagolix (ABT-620)	**Phase of Development:** 3
Name of Active Ingredient: Elagolix sodium	**Date of Protocol Synopsis:** 25 September 2017
Protocol Title: A Phase 3 Study to Evaluate the Efficacy and 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 efficacy, safety and tolerability of elagolix 300 mg BID in combination with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD), versus placebo to reduce heavy menstrual bleeding (HMB) associated with uterine fibroids in premenopausal women 18 to 51 years of age, and 2) to characterize the impact of E2/NETA on the safety/tolerability [including bone mineral density (BMD) and other hypoestrogenic side effects] and efficacy of elagolix.	
Investigators: Multicenter trial. Investigator information is on file at AbbVie.	
Study Sites: Approximately 125 sites	
Study Population: Premenopausal female subjects (aged 18 to 51 years, inclusive) with uterine fibroids and HMB (> 80 mL blood loss per menstrual cycle).	
Number of Subjects to be Enrolled: Approximately 400	
Methodology: This Phase 3, randomized, double-blind, multicenter, placebo-controlled study is designed to evaluate the efficacy, safety and tolerability of elagolix alone and in combination with E2/NETA in the management of premenopausal women with HMB associated with uterine fibroids. Approximately 400 subjects will be randomized in a 1:1:2 ratio of placebo to active treatment alone and in combination with E2/NETA to one of the following three treatment groups: • placebo (n = 100) • elagolix 300 mg BID (n = 100) • elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) QD (n = 200)	
Study Duration: The total duration for this study is approximately 21 months. The study consists of 4 periods: • Washout Period prior to Screening (only applicable if subject is taking hormonal medication at the time of consent; duration of washout depends on the type of hormonal medication). • Screening Period – approximately 2.5 to 3.5 months prior to first dose of study drug. • Treatment Period – 6-month treatment duration. • Post-Treatment Follow-Up Period – 12-month period, OR instead of entering the Post-Treatment Follow-Up Period, subjects may enter into an extension study (Study M12-816) if they are willing and qualify, based on safety parameters, to receive an additional 6 months of treatment, followed by 12 months of follow-up.	

Washout Period:

Following informed consent, subjects, who are taking or were taking exclusionary medications such as hormonal medications or antifibrinolytics prior to screening that require washout, must enter a Washout Period. Subjects must complete the Washout Period and have had at least 1 menses after completion of washout, prior to entering the Screening Period. The duration of the required washout period is based on the excluded hormonal medication that the subject is currently taking, or was taking. Procedures such as medical, social and gynecological history, a complete physical examination (including height and weight) with vital signs and urine pregnancy testing, protocol-related adverse event review will be performed and current medications will be documented. Contraceptive counseling will be provided, and contraceptives dispensed, as necessary. 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.

Screening Period:

Following informed consent (if Washout was not required), subjects will enter into an approximate 2.5- to 3.5-month Screening Period to establish eligibility based on inclusion and exclusion criteria. A pelvic ultrasound (TAU and TVU) will be performed to confirm the presence and size of qualifying uterine fibroids and uterine volume and to rule out exclusionary ovarian cysts. In addition to the ultrasound, a saline infusion sonohysterography (SIS) will be conducted to rule out exclusionary gynecological disorders such as pedunculated submucosal fibroids and endometrial polyps. An endometrial biopsy will be performed to rule out endometrial pathology. A mammogram in subjects who will be 39 years of age or older at the time of randomization will be performed unless the subject had a mammogram performed within 3 months prior to Screening. DXA scans will be performed to evaluate bone mineral density (BMD) for determination of eligibility. 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 on days with menstrual bleeding or spotting, and must return the products to the site within approximately 5 days after cessation of menses. **Subjects must be instructed to collect and return all used or worn products even if there is no visible blood on the products.** Subjects will also complete the Screening-Baseline Columbia Suicide Severity Rating Scale (C-SSRS) questionnaire to assess suicidal behavior and ideation.

Treatment Period:

The Treatment Period begins with Day 1, which will occur between 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.

Subjects will be randomized to receive either placebo (n = 100), elagolix 300 mg BID (n = 100) or elagolix 300 mg BID plus E2/NETA (n = 200). All subjects will self-administer study medication or matching placebo twice daily (in the morning and in the evening approximately 12 hours apart) orally throughout the 6-month Treatment Period. Subjects randomized into the study will visit the site during the 6-Month Treatment Period on Day 1, and then monthly (28-day intervals), at Month 1 through Month 6. Additional study visits may occur either for subjects returning their sanitary products for analysis of alkaline hematin at a Product Collection Visit or for a Premature Discontinuation visit.

Treatment Period (Continued):

Treatment Period Assessments:

Sanitary product collection kits will continue to be dispensed at all Treatment Period visits. Subjects will be required to collect all sanitary products on days with menstrual bleeding or spotting and return them to the clinical study site, either during a scheduled monthly visit or at a Product Collection Visit. **Subjects must be instructed to collect and return all used or worn products even if there is no visible blood on the products.** If a subject does not return a sanitary product collection keg at any site visit (scheduled monthly visit or Product Collection visit), the Site Staff will administer the Uterine Bleeding Questionnaire (UBQ) to record if she had any bleeding or spotting since the last study visit. If the subject had bleeding or spotting since the last study visit, the Site Staff will record the subjects response indicating why she did not collect products or return a sanitary product collection keg.

A pelvic ultrasound will be performed in all subjects at Day 1, Month 3, Month 6 or Premature Discontinuation Visit, if applicable, to assess volume of the largest fibroid, uterine volume, endometrial thickness and potential presence of ovarian and uterine pathology. During the Treatment Period, Magnetic Resonance Imaging (MRIs) in a subset of subjects will be conducted at Day 1 and Month 6 or Premature Discontinuation Visit, if applicable to assess fibroid and uterine volume. An endometrial biopsy will be performed in all subjects at the Month 6 or premature discontinuation visit. It is recommended that the pelvic ultrasound, MRI (if applicable) and endometrial biopsy procedures be performed within the – 15 day procedure window).

Subjects will be asked to complete several patient-reported outcome questionnaires, such as the EQ-5D-5L, Uterine Fibroid Symptom Questionnaire (UFS-QoL), Work Productivity and Activity Impairment (WPAI) questionnaire, Health Care Resource Utilization questionnaire (HCRU), C-SSRS – Since Last Visit questionnaire and Patient Global Impression of Change (PGIC), based on bleeding and non-bleeding uterine fibroid symptoms. Site Staff will administer the Uterine Bleeding Questionnaire (UBQ), as applicable and the HCRU. The Investigator will complete the Physician Surgery Questionnaire.

Pregnancy (urine and/or serum) tests will be performed at each visit throughout the study. Subjects will be counseled at each visit on appropriate and effective forms of dual non-hormonal contraceptives to promote pregnancy prevention.

During the Treatment Period, blood samples will be collected for assay of serum estradiol and progesterone, and to measure plasma concentrations of elagolix and NETA.

Subjects will provide blood samples for Clinical Safety Labs, (including lipid panel) and for subjects who consent, a DNA pharmacogenetic sample will be collected on Day 1 and an RNA pharmacogenetic sample will be collected on Day 1, Month 1, Month 3 and Month 6 or Premature Discontinuation.

DXA scans will be obtained at Month 6 of the Treatment Period. Sites will be encouraged to schedule the Month 6 DXA as early as possible within the – 15-day Month 6 treatment window, allowing for the evaluation of BMD prior to entering post-treatment follow-up or the extension study, Study M12-816. Subjects with BMD decrease < 8% in spine, total hip and femoral neck will be eligible for entry into the extension study. Subject's with ≥ 8% decrease in BMD in the spine, total hip or femoral neck at Month 6 of the Treatment Period are ineligible for entry into the extension study and will enter into the Post-Treatment Follow-up Period.

Post-Treatment Follow-Up Period:

Eligible subjects who complete the 6-month Treatment Period, may, following consent, enter a separate extension study for 6 additional months of treatment with elagolix (for further details, refer to the Study M12-816 protocol synopsis). Subjects who prematurely discontinue from treatment, decline to participate in, or do not qualify for the extension study, will enter 12-month the Post-Treatment Follow-Up Period.

For subjects entering the 12-month Post-Treatment Follow-Up Period, visits will be conducted either by phone or on-site from Month 1 through Month 12. (Subjects who prematurely discontinue from the Treatment Period prior to the Month 3 Study visit, are not required to have the pelvic ultrasound, MRI [if applicable] or DXA [unless the reason for discontinuation was due to BMD decrease or occurrence of fracture] performed in the Post-Treatment Follow-up Period and will complete the study at the Post-Treatment Follow-up Month 6 visit.) Post-Treatment Follow-up Months 1, 3, 6, 9 and 12 are on-site visits while Post-Treatment Follow-up Months 2, 4, 5, 7, 8, 10 and 11 are Phone Visits.

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 and will remind subjects of the importance of consistent use of appropriate and effective dual non-hormonal contraception through the Post-Treatment Follow-Up Period. Subjects may begin taking hormonal contraception or Tranexamic Acid (Lysteda, Cyklokapron, Cyclo-f) after completing the Post-Treatment Follow-Up Month 2 Visit and having returned to first full menses in the Post-Treatment Follow-up Period.

Subjects will be required to collect sanitary products for the first full menses in the Post-Treatment Follow-up Period. Subjects will return the sanitary products at a Product Collection Visit within approximately 5 days after cessation of bleeding or spotting.

During the Post-Treatment Month 3 and Post-Treatment Month 6 on-site visits, procedures such as TAU, TVU, MRI (if applicable), DXA, clinical safety labs and pregnancy testing will be performed. At the Post-Treatment Period Month 12 visit, procedures including vital signs, lipid panel, Apolipoprotein A and B and DXA will be performed.

Adverse event and concomitant medication review will be conducted at all visits during the Post-Treatment Follow-Up Period, including the phone visits.

Central Laboratory and Central Imaging Vendors:

DXA, Ultrasound, SIS, MRI (if applicable), safety clinical lab samples including Apo A, and Apo B, endocrine panels, and alkaline hematin will be analyzed/evaluated using central laboratories or vendors. Assays for PK, PD and PG will be analyzed at AbbVie.

Analysis of Menstrual Blood Loss:

This study will utilize the alkaline hematin (AH) method for measuring MBL from screening through the first full menses in the Post-Treatment Follow-up Period. Alkaline hematin is an objective and reliable measurement of total MBL based on the quantitation of menstrual blood collected on sanitary products.

Key Criteria for Inclusion/Exclusion:

Key Inclusion Criteria:

1. Subject has voluntarily signed and dated the informed consent form (ICF), approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to washout (if applicable), or initiation of any screening or study-specific procedures.
2. Subject is a premenopausal female 18 to 51 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 fibroid present meets at least one of the following criteria:
   - Intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter).
   - Subserosal fibroid ≥ 4 cm.
   - 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 screening menses as measured by the alkaline hematin method.
5. Subject has a Screening FSH level of < 35 mIU/mL (35 IU/L).
6. 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.
7. Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Washout (if applicable), Screening, Treatment and Post-Treatment Follow-Up Periods. (Subject may start hormonal contraception after completion of the Post-Treatment Month 2 Visit and return to first full menses). 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 (including ligation and blockage methods such as Essure®), 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.
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.
11. Subject has not taken exclusionary hormonal therapies within the specified washout interval prior to the initiation of any screening procedures and must have returned to at least 1 menses after completion of washout, prior to initiation of any screening procedures.

Key Criteria for Inclusion/Exclusion (Continued):

Rationale For Inclusion Criteria:

1	This is standard criterion in accordance with harmonized Good Clinical Practice (GCP)
2, 3, 4, 5	These criteria were selected to ensure an appropriate subject population of premenopausal women with HMB associated with uterine fibroids. (prognostic and predictive)
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. (prognostic and risk)
8, 9	These are standard criteria to ensure general good health and the safety of the subjects. (risk)
10, 11	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications. (predictive and risk)

Key Exclusion Criteria:

1. Subject has had menstrual cycles that are > 38 days in length for the past 3 months prior to Screening.
2. 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 initial pelvic ultrasound shows a simple ovarian cyst > 5 cm and ≤ 7 cm an ultrasound of the ovaries may be repeated in 4 to 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 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 or country guidelines) has a Pap smear result that meets exclusionary criteria.
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 < 8 g/dL (subjects with initial screening hemoglobin results < 8 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.

Key Criteria for Inclusion/Exclusion (Continued):

Key Exclusion Criteria (Continued):

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 moderate to severe hepatic impairment including aspartate aminotransferase (ASAT/SGOT) or alanine aminotransferase (ALAT/SGPT) 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 or ECG with QT interval corrected for heart rate (QTc) > 450 msec at Screening using either Fridericia's correction (QTcF) or Bazett's correction (QTcB).
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 24 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 1.5 or more standard deviations below normal (T-score ≤ –1.5).
    - 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).
    - 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).
    - History of 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.
17. Subject has a history of major depression or post-traumatic stress disorder (PTSD) 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) at Screening or Day 1, prior to randomization.

Key Criteria for Inclusion/Exclusion (Continued):

Key Exclusion Criteria (Continued):

19. Subject has a clinically significant medical condition that requires intervention **OR** an unstable medical condition that makes the subject an unsuitable candidate for the study in the opinion of the investigator.
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. Subject has history of or active malignancy (except basal cell carcinoma of the skin) with or without systemic chemotherapy.
23. Subject has a history of clinically significant condition(s) or documented history of a severe, life-threatening or other significant sensitivity to any drug.
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 cannot tolerate estrogen- or estrogen plus progestin-containing preparations (e.g., oral contraceptives), or these preparations are contraindicated due to medical reasons.
26. Subject used any known moderate or strong inducers (e.g., cyclosporine, rifampin, carbamazepine, St. John's Wort) of cytochrome P450 3A (CYP3A) as indicated in Table 3 within 1 month prior to randomization.
27. Subject is using a copper intra-uterine device (CU-IUD) or levonorgestrel intrauterine system (LNG-IUS). If LNG-IUS is removed and subject completes washout or the CU-IUD is removed and the subject returns to 1 menses after completion of washout for LNG-IUS or after removal of the CU-IUD, the subject can be screened for eligibility.
28. 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 injectable (for occasional use) corticosteroids are allowed.
29. Subject is using oral retinoid preparations such as Accutane® (isotretinoin). Topical isotretinoin applications are permitted.
30. Subject has a history of drug abuse and/or alcohol abuse within 12 months prior to Screening.
31. Subject was previously enrolled (randomized) in an elagolix study.
32. 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 5 times the investigational drug half-life, whichever is longer, prior to Screening procedures.
33. 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.

Key Criteria for Inclusion/Exclusion (Continued):

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. (prognostic and predictive)
5 – 13, 15 – 23, 29, 30	These are standard criteria to ensure general good health and the safety of the subjects. (prognostic and risk)
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. (risk)
31, 32	This criterion was selected to avoid bias for the evaluation of efficacy and safety by prior participation in an elagolix study. (predictive and risk)
25 – 28	These criteria were selected to ensure that efficacy can be adequately assessed. (predictive and risk)
33	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. (predictive)

Investigational Products:	Elagolix sodium 300 mg tablets Estradiol 1.0 mg/norethindrone acetate 0.5 mg
Doses:	Placebo Elagolix 300 mg BID alone Elagolix 300 mg BID plus estradiol/norethindrone acetate (E2 1.0 mg/NETA 0.5 mg) QD
Reference Therapy:	Placebo to match Elagolix; Placebo to match E2/NETA
Mode of Administration:	Oral

Duration of Treatment: Subjects will receive 6 months of treatment.

Duration of Post-Treatment Follow-Up: 12 months (applicable to subjects not entering the extension study, Study M12-816).

Criteria for Evaluation:

Efficacy:

The analysis will compare 6 months of treatment with elagolix with and without add-back therapy, estradiol/norethindrone acetate (E2/NETA) to placebo.

Criteria for Evaluation (Continued):

Primary Efficacy Endpoint:

The primary endpoint will be the percentage of subjects meeting a composite endpoint consisting of these two bleeding assessments:

- MBL volume < 80 mL during the Final Month (the last 28 days of treatment), AND
- 50% or greater reduction in MBL volume from baseline to the Final Month (the last 28 days of treatment).

A subject who prematurely discontinues the study drug due to adverse events, "lack of efficacy," or "requires surgery or invasive intervention for treatment of uterine fibroids" will be considered as a non-responder regardless whether she meets the two aforementioned responder criteria or not.

Secondary Efficacy Variables:

- MBL volume assessed using alkaline hematin methodology and UBQ
- Suppression of bleeding
- Hemoglobin concentration
- Fibroid and uterine volume
- UFS-QoL Questionnaire
- EuroQol (EQ-5D-5L) Questionnaire
- Health Care Resource Utilization (HCRU) Questionnaire
- Patient Global Impression of Change (PGIC) Questionnaires
- Work Productivity and Activity Impairment (WPAI) Questionnaire

Safety:

Safety evaluations include physical examination, vital signs, ECG, BMD changes, endometrial assessment (endometrial thickness and biopsy), clinical laboratory tests (hematology, chemistry, urinalysis, lipid panel) and adverse event monitoring.

Statistical Methods:

Efficacy:

Primary Efficacy Analysis:

The primary analysis will be based on the modified intent-to-treat (mITT) analysis set which is comprised of all randomized subjects who took at least one dose of the study drug and have at least one post-baseline visit in this study.

The baseline MBL volume will be defined as the mean of MBL volume from the qualified menstrual cycles during the Screening Period prior to the first study drug dose date, in which the total MBL volume is from all validated and non-validated sanitary products that subjects returned and where the total MBL volume of validated sanitary products only (excluding non-validated sanitary products) is greater than 80 mL. All menstrual cycles during the Screening Period in which the total MBL volume of validated sanitary products only is less than or equal to 80 mL are not qualified to be considered for baseline.

Final Month is defined as the last 28 days of treatment prior to and including the last dose date.

The primary endpoint will be analyzed using a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate. Missing Final Month MBL volume will be imputed using multiple imputation.

Statistical Methods (Continued):

Efficacy (Continued):

Primary Efficacy Analysis (Continued):

The primary efficacy comparison will be between the elagolix 300 mg BID plus E2/NETA group and the placebo group. Therefore, no multiplicity adjustment is necessary.

Analyses for Secondary Efficacy Variables:

In general, data will be summarized for the Treatment Period and Post-Treatment Period separately. Data for the Treatment Period will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

The percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline during the Treatment Period will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group. Also, the individual component (the percentage of subjects with MBL volume of < 80 mL as well as the percentage of subjects with ≥ 50% reduction in MBL volume from baseline) will be summarized.

The change and percent change from baseline in MBL volume to each month and to the Final Month, will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

The percentage of subjects with suppression of bleeding and the percentage of subjects with amenorrhea will be summarized by monthly intervals throughout the Treatment Period. In addition, the cumulative percentage of subjects with suppression of bleeding and the cumulative percentage of subjects with amenorrhea will be summarized by treatment group.

The change from baseline to monthly intervals in number of bleeding days will be summarized by treatment group. In addition, the change from baseline in total number of sanitary products will be summarized by treatment group.

The change and percent change from baseline in hemoglobin concentration will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

The change and percent change from baseline in primary fibroid volume, total fibroid volume, and uterine volume will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group. The change from baseline for quality of life assessments (e.g., UFS-QoL, EQ-5D-5L) will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

For the PGIC-MB and PGIC-NBUFS, the number and percentage of subjects in each response category will be summarized by treatment group.

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, chemistry, urinalysis, lipid panel, vital signs and endometrial biopsy variables will be summarized.

Statistical Methods (Continued):

Safety (Continued):

To evaluate BMD change, the percent change from baseline to Month 6 in the Treatment Period using aggregated data from two pivotal studies (Studies M12-815 and M12-817) will be compared between each elagolix treatment group and the placebo group as well as between the elagolix 300 mg BID group and the elagolix 300 mg BID plus E2/NETA group using analysis of co-variance (ANCOVA) with treatment as the main effect and baseline BMD as a covariate. Two-sided 95% confidence intervals will be constructed for the differences in percent change from baseline to Month 6 in BMD.

Sample Size:

Approximately 400 subjects will be randomized (1:1:2) to placebo (N = 100), elagolix 300 mg BID (N = 100), or elagolix 300 mg BID plus E2/NETA (N = 200) for 24 weeks of dosing. The sample size will provide at least 90% power to detect a difference between the elagolix 300 mg BID plus E2/NETA group and the placebo group in the percentage of subjects with MBL volume < 80 mL during the Final Month (the last 28 days of treatment) and 50% or greater reduction in MBL volume from baseline to the Final Month under the assumption of responder rates being 60% and 30% for elagolix 300 mg BID plus E2/NETA and placebo, respectively.

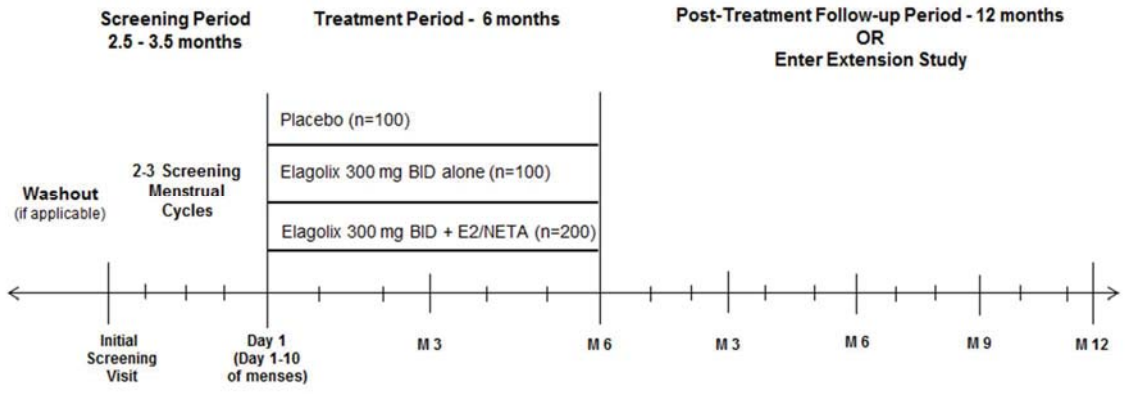
Pharmacokinetic:

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. Exposure-response analyses may be conducted as appropriate.

Pharmacodynamic:

Serum concentrations of estradiol, progesterone, FSH, and LH will be listed for each subject by visit day and dose regimen.

Study Schematic:



1.3 List of Abbreviations and Definition of Terms

Abbreviations

Ab	Antibody
ABT	Abbott/AbbVie
AE	Adverse Event
AGC	Atypical Glandular Cells
AH	Alkaline Hematin
APO A	Apolipoprotein A
APO B	Apolipoprotein B
ASC-H	Atypical Squamous Cells cannot exclude High grade squamous intraepithelial lesion
ASC-US	Atypical Squamous Cells of Undetermined Significance
AESI	Adverse Event of Special Interest
BID	Twice daily (bis in die)
BI-RADS	Breast Imaging Reporting and Data System
BMD	Bone Mineral Density
BUN	Blood Urea Nitrogen
CIN	Cervical Intraepithelial Neoplasia
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CU-IUD	Copper IUD
CYP3A	Cytochrome P450 3A
D&C	Dilation and curettage
DNA	Deoxyribonucleic acid
DXA	Dual energy X-Ray Absorptiometry
E2	Estradiol
ECG	12-Lead Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol-5D-5L
FDA	US Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

GLP	Good Laboratory Practices
GnRH	Gonadotropin releasing hormone
HAV-IgM	Hepatitis A Virus Immunoglobulin M
HBsAg	Hepatitis B Surface Antigen
HCRU	Health Care Resource Utilization
HCV Ab	Hepatitis C Virus Antibody
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
ICL	Imaging Core Lab
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
K_2EDTA	K_2-ethylenediaminetetraacetic acid
LDL	Low-density Lipoprotein
LH	Luteinizing Hormone
LNG-IUS	Levonorgestrel Intrauterine System
LSIL	Low-grade squamous intraepithelial lesion
M	Month (visit)
MAD	Multiple Ascending Dose
MBL	Menstrual Blood Loss
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Cell volume of RBC
MedDRA	Medical Dictionary for Regulatory Activities

MRI	Magnetic Resonance Imaging
NETA	Norethindrone acetate
NBI	Neurocrine Biosciences Inc
P	Progesterone
Pap	Papanicolau
PCV	Product Collection Visit
PD	Premature Discontinuation
PGIC-MB	Patient Global Impression of Change – Menstrual Bleeding
PGIC-NBUFS	Patient Global Impression of Change – Non-Bleeding Uterine Fibroid Symptoms
PID	Pelvic Inflammatory Disease
P-gp	P-glycoprotein
PK	Pharmacokinetic
POC	Proof-of-Concept
PRO	Patient Reported Outcome
PSQ	Physician Surgery Questionnaire
PTSD	Post-Traumatic Stress Disorder
QD	Once a day (quaque die)
QoL	Quality of Life
RANKL	Receptor activator of nuclear factor-κB ligand
RBC	Red Blood Cell
RR	Respiration Rate
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT/ASAT	Serum glutamic-oxaloacetic transaminase/aspartate aminotransferase
SIS	Saline Infusion Sonohysterography
SGPT/ALAT	Serum glutamic-pyruvic transaminase/alanine aminotransferase
SPRM	Selective Progesterone Receptor Modulator
TA MD	Therapeutic Area Medical Director
TAU	Transabdominal Ultrasound
TDD	Total Daily Dose
TBG	Thyroxine-Binding Globulin
TSH	Thyroid Stimulating Hormone
TEAEs	Treatment-emergent adverse events

TVU	Transvaginal Ultrasound
UBQ	Uterine Bleeding Questionnaire
UFS-QoL	Uterine Fibroid Symptom Quality of Life Questionnaire
WBC	White Blood Cells
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

Pharmacokinetic and Statistical Abbreviations

ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AUC	Area under the plasma concentration-time curve
C_{max}	Maximum concentration in plasma
LOCF	Last Observation Carried Forward
NOAEL	No observed-adverse-effect levels
PD	Pharmacodynamic
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
T_{max}	Time to maximum observed plasma concentration

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 approximate 2.5 to 3.5 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.
Monthly Visits: Treatment Period Months 1 through 6 and Post-Treatment Period Months 1 through 12	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 (either during screening or the treatment period); visits should occur within approximately 5 days after the last sanitary product was collected during a bleeding and/or spotting episode.
Home Product Collection Visits (Home PCVs)	Product Collection Visit conducted at home by a Home Health Care Agent who will go to the subject's home to draw a venous blood sample and retrieve the collection keg to return to the study site.
Heavy Menstrual Bleeding	Menorrhagia or > 80 mL blood loss
Vasomotor Symptoms	e.g., hot flush and night sweats

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

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.[1,2] 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 > 80 mL per menstrual cycle)[1] is extremely inconvenient, can significantly impact quality of life and may lead to iron-deficiency anemia.

The choice of treatment is based on individual symptoms, patient preference, and the desire to preserve either fertility or the uterus or both. Historically, hysterectomy or myomectomy were the preferred treatment options for women with symptomatic uterine fibroids.[2] However, surgery is also associated with risks such as infections, bleeding complications, thromboembolic effects, scarring/adhesions, and even increased mortality.[6] As more women delay pregnancy into their 30s and 40s, there is a growing need for alternatives to surgical treatments, especially hysterectomy. To meet this demand, during the past 2 decades many new uterus-sparing therapies have been proposed and studied including semi-invasive procedures, such as uterine artery embolization and magnetic resonance imaging (MRI)-guided high-intensity focused ultrasound ablation therapy as well as nonsurgical, medical treatments. There is no long-term medical treatment for

symptomatic uterine fibroids. Treatment with GnRH agonists such as Lupron® is effective but induces full gonadal suppression and menopause-like symptoms that limit their use to 3 months of presurgical treatment. High-dose progestins, oral contraceptives and tranexamic acid (Lysteda®-an antifibrinolytic drug) are used for short-term management of heavy uterine bleeding only. Recently, the selective progesterone receptor modulator (SPRM), ulipristal acetate, has been approved in the EU as a short-term preoperative treatment, as well as an extended intermittent treatment of women with of 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 is an orally active, non-peptide (GnRH) antagonist that is being developed by AbbVie for the management of endometriosis-related pain and the chronic management of 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 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 and is also discussed in lesser detail in Section 3.2.1 and Section 3.2.2.[7]

The initial 3-month, Phase 2a, dose-finding, Proof-of-Concept (POC) study (Study M12-663) evaluated total daily doses (TDDs) of elagolix of 200, 400, and 600 mg in premenopausal women with HMB associated with uterine fibroids. Data from this study indicated that an elagolix TDD of 600 mg best met the agreed-upon dose selection criteria for Phase 2b and Phase 3 (predicated on a dose in Phase 2a that provided the most robust response [responder rates of approximately > 80% for the composite bleeding assessment] and an acceptable safety and bleeding profile for the majority of women). It was known that to support long-term dosing with elagolix at these higher doses, low dose hormonal add-back therapy would be required to mitigate bone loss and minimize other hypoestrogenic adverse events, e.g., hot flush.

Subsequently, a 6-month safety and efficacy Phase 2b study (Study M12-813) evaluating elagolix TDD of 600 mg (administered as 300 mg BID [twice daily] in Cohort 1 or 600 mg QD in Cohort 2) with and without add-back therapy was conducted. As add-back therapy, the study evaluated two doses of E2/NETA (low dose, 0.5 mg/0.1 mg and standard dose, 1.0 mg/0.5 mg). Preliminary results from Cohort 1 demonstrated that treatment with elagolix 300 mg BID alone and in combination with E2/NETA provided robust efficacy in controlling HMB associated with uterine fibroids and provided an acceptable safety/tolerability profile that could potentially support the proposed chronic use indication. While similar efficacy results were noted in Cohort 2 (elagolix 600 mg QD), review of the totality of data (preclinical, Phase 1 and Phase 2) comparing two dosing regimens support selection of the 300 mg BID + standard dose E2/NETA as the regimen for Phase 3.

Additional details on rationale for dose selection are included in Section 5.6.4.

3.2.1 Preclinical Experience

3.2.1.1 Toxicology

Elagolix has been well characterized in repeated-dose animal toxicity studies of up to 15 weeks in mouse, 28 weeks in rat, 39 weeks (9 months) in dog and 13 weeks in

monkey. The safety margin for the 200 mg BID human dose for the endometriosis indication is approximately 8.6 (28 week rat study) and 7.5 (9 month dog study).

There were no significant findings from in vitro and in vivo genotoxicity studies. Also, there was no significant increase in tumors in the 2-year mouse carcinogenicity study with elagolix sodium. In the 2-year rat carcinogenicity study, increase in thyroid or liver tumors was rat specific with no risk anticipated for human.

Elagolix is not teratogenic (no fetal abnormalities in preclinical studies) based on data from the rat and rabbit Segment II studies. However, there were non-teratogenic findings, e.g., observations of abortions in rabbit and post-implantation loss in rat at higher doses. These could either be due to maternal toxicity or related to indirect pharmacological activity.

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 Edition 15 of the elagolix Investigator's Brochure (April 2016 or the most recent version) for the complete information on clinical studies, exposure to study drug, and safety.

Clinical Program Overview

As of 31 January 2016, a total of 3,417 subjects have received at least 1 dose of elagolix in clinical studies conducted by NBI and AbbVie (30 Phase 1 studies, 6 Phase 2 endometriosis studies, 2 Phase 2 uterine fibroid studies [Study M12-663 and M12-813], 2 Phase 3 endometriosis studies [Study M12-665 and M12-667] and 2 ongoing Phase 3 endometriosis extension studies [Studies M12-667 and M12-821]). More than 1,000 of these subjects were dosed for ≥ 6 weeks. Of the 3,417 subjects, 95 were healthy men, 795 were healthy women, 1,857 were women with endometriosis, 645 were women with uterine fibroids, 16 were women with hepatic impairment, and 9 were women with renal

impairment. In ongoing studies (including 2 extension studies mentioned above and excluding Study M12-671), more than 1,625 subjects have received at least 1 dose of elagolix.

Twelve Phase 1 clinical studies (7 in healthy men and 5 in healthy women) and 6 Phase 2 studies (in women with endometriosis) were completed by NBI. To date, 18 Phase 1 studies have been completed by AbbVie. The Phase 3 endometriosis registration program consists of 2 replicate 6-month pivotal studies, Study M12-665 and Study M12-671 and 2 extension studies, Study M12-667 and Study M12-821, respectively. 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.

Clinical Pharmacokinetic and Pharmacodynamic Summary

Clinical pharmacokinetic (PK) studies indicate that elagolix is rapidly absorbed from the gastrointestinal (GI) tract with time to maximum plasma concentration (T_{max}) of approximately 1 hour for immediate release (IR) tablet formulation. The following points are key findings of elagolix PK:

- Elagolix exposure (area under the plasma concentration versus time curve [AUC] and maximum concentration in plasma [C_{max}]) appears to be approximately dose-proportional across the daily dose range studied (25 to 400 mg). At single daily doses of 600 mg and above, more than dose proportional increases in elagolix exposures were observed.
- Elagolix displays biphasic disposition with a terminal elimination half-life of approximately 4 to 6 hours. Little or no accumulation resulted from twice daily (BID) (400 mg BID) or once daily (QD) (400 mg QD) dosing at steady state.
- Food decreases the AUC of the immediate-release tablet formulation by approximately 25%.

- Elagolix is a substrate of CYP3A and P-gp and may be a weak inducer of CYP3A enzymes.
- Elagolix is primarily excreted in feces as metabolites (64%) and parent compound (26%). Less than 3% is excreted unchanged in the urine. Plasma exposure of elagolix metabolites was low (< 3% of each metabolite) relative to the parent.

Pharmacodynamic data from the AbbVie multiple-ascending dose (MAD) study, Study M12-790, in premenopausal healthy female subjects showed a dose-dependent suppression of E2, reaching maximum suppression at approximately 200 mg BID. Anovulatory progesterone levels were observed through Day 21 in all subjects at doses as low as 100 mg BID. In addition, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) decline in a dose dependent manner, with maximal suppression and near maximal suppression, respectively, at 300 mg BID. The elagolix 400 mg BID dose does not appear to result in substantial additional E2 suppression compared with the 300 mg BID dose.

Effects on Ovulation

Elagolix is not a contraceptive and data on ovulation rates from the 3-month folliculogenesis study, Study M12-673, showed that the 100 mg BID, 150 mg QD, and 200 mg QD doses do not appear to differentiate. The percentage of subjects with at least 1 ovulation during the 3 months of elagolix treatment was 47.4% to 57.1%, and the percentage of subjects with ovulation was 28.1% to 33.3% within each month (28-day period). In contrast, when ovulation rates are counted by subject or by month, the 200 mg BID dose appears to decrease ovulation rates to almost half of that observed with the 150 mg QD dose. 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 ovulation rate decreased further to approximately 10%.

Summary of Safety Findings

Adverse Events Across Elagolix Studies

As of 31 January 2016, the most common adverse events overall in the 3,417 subjects who received elagolix across all clinical studies were hot flush (598/3,417; 17.5%), headache (546/3,417; 16.0%), and nausea (411/3,417; 12%). These are also the adverse events that most commonly resulted in discontinuation from study: hot flush in 33 subjects (1.0%), headache in 15 subjects (0.4%), and nausea in 16 subjects (0.5%).

Adverse Events in Phase 2 Studies in Uterine Fibroids

Study M12-663

Preliminary data from the completed Phase 2a POC study, Study M12-663, show that the most commonly reported adverse event in all the elagolix treatment cohorts was hot flush; this was reported for approximately 45% to 63% of the subjects in the cohorts in which elagolix was administered alone. The use of both add-back therapies [elagolix 200 mg BID + LD (low-dose) E2/NETA QD and elagolix 300 mg BID + cyclical EP] was associated with an approximate 30% lower overall incidence of hot flush that was approximately 30% lower relative to the corresponding elagolix treatment regimen alone.

Other than hot flushes, the only other adverse events in the elagolix 300 mg BID group reported for more than 2 subjects were headache (6 subjects, 20%), and abdominal pain and dizziness (3 subjects each, 10%). At the 600 mg QD dose of elagolix, the presence of nausea (9 subjects), headache (9 subjects), dizziness (6 subjects), and back pain (5 subjects) was more prevalent than in the remaining elagolix treatment cohorts.

Study M12-813

Preliminary data from the completed Phase 2b study, Study M12-813, 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%).

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

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

In the completed Phase 2 studies in uterine fibroids, there was a higher percentage of women experiencing cutaneous/hypersensitivity events and hot flush with elagolix treatment compared with placebo. Adverse events of special interest are monitored continuously in all clinical studies.

Serious Adverse Events Across Elagolix Studies

As of 31 January 2016, 129 serious adverse events have been reported by 92/3, 417 (2.7%) subjects who received elagolix. Serious adverse events in all completed studies and in ongoing Studies M12-667 and M12-821 through the data cutoff date of 31 January 2016 are captured in the analysis for this update. The most common serious adverse event was pelvic pain occurring in 8 subjects (0.2%) followed by induced abortion and endometriosis, each occurring in 5 subjects (0.1%), and abdominal pain and uterine leiomyoma, each occurring in 4 subjects (0.1%).

Among women participating in elagolix clinical trials, one subject delivered an infant with congenital pneumonia. During the Phase 2 clinical development program in endometriosis, there were 2 pregnancy-related serious adverse events (congenital malformations, i.e., 1 cleft palate and 1 tracheoesophageal fistula), which occurred during treatment and were assessed as unrelated to elagolix.

In the completed Phase 2a study in women with HMB associated with uterine fibroids, there were 2 serious adverse events of prolapsed uterine fibroid.

Based on the preliminary results of Cohort 1 of the Phase 2b study in women with HMB associated with uterine fibroids, as of 31 January 2016, there were 7 serious adverse events that either occurred during the Treatment Period or within 30 days of last dose in 8 subjects randomized to receive active treatment. Four events occurred in the elagolix 300 mg BID alone arm [pulmonary embolism, deep vein thrombosis (both events experienced by the same subject), menorrhagia and endometrial adenocarcinoma]; 2 events occurred in the 300 mg BID plus low-dose activella arm (uterine leiomyoma and hypertension), and 1 event occurred in the 300 mg BID plus standard-dose activella arm (anemia).

Effects of Elagolix on Bone Mineral Density (BMD)

The effects of elagolix 300 mg BID alone and in combination with low-dose and standard dose E2/NETA were evaluated in the 6-month Phase 2b study (Study M12-813). 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.

Preliminary results from the 6-month Phase 2b uterine fibroid study, Study M12-813, 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, 25% had > 5% to < 8% BMD decrease, and 8% had a ≥ 8% BMD decrease.

While the addition of low-dose E2/NETA partially prevented BMD loss at the lumbar spine at Month 6 of treatment compared to the elagolix alone group (mean change from baseline –1.5% versus –3.6%), the E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) more substantially mitigated BMD loss at the lumbar spine at Month 6 compared with the elagolix alone group (mean change from baseline –0.1% versus –3.6%). In the E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) group 8.2% of subjects had a 3 to ≤ 5% BMD decrease, 1 subject (2%) had a 5% – 8% BMD decrease and no subjects (0%) had ≥ 8% BMD decrease at the lumbar spine.

Effects of Elagolix on Clinical Laboratory Parameters

Data from the Phase 2 studies with elagolix in women with uterine fibroids showed dose-dependent increases in serum lipid parameters, corresponding to the degree of estrogen suppression and similar to those seen with other GnRH analogs. Changes in serum lipids, in particular total cholesterol and low-density lipoprotein cholesterol (LDL-C), were observed in this study, similar to those observed in postmenopausal women[8] 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. Ongoing clinical trials with elagolix suggest similar findings, again which are consistent with those noted with other GnRH analogs. While the significance of these lipid changes in premenopausal women with low-risk baseline lipid values is unknown, further monitoring and evaluation is needed. 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.

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.

Study M12-813

Preliminary 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, and 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

Study M12-813

Endometrial biopsies were conducted at Baseline and at Month 6 in Study M12-813. Preliminary 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.

Preliminary 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.

3.2.3 Pregnancy in Elagolix Studies

Pregnancies (Across the Entire Elagolix Clinical Development Program)

The mechanism of action of elagolix, bleeding pattern, and the indirect evidence for follicular escapes (high E2 and progesterone values) indicate that elagolix does not consistently inhibit ovulation and as discussed in Section 3.2.2, Clinical Pharmacokinetic and Pharmacodynamic Summary, elagolix is not a contraceptive.

As of 05 February 2016, 172 pregnancies have been reported among women participating in elagolix clinical trials, including 104 that occurred off-treatment (58 during Screening and 46 during Post-Treatment [had a conception date more than 30 days after the last dose of study drug]) and 68 On-Treatment (i.e., had conception date during the Treatment Period with study drug or were deemed to have a conception date within 30 days after the last dose of study drug). Among the 68 on-treatment pregnancies, 21 subjects had no exposure to elagolix (20 subjects treated with placebo only and 1 subject treated with oral contraceptives only). The remaining 47 on-treatment pregnancies were in elagolix-treated subjects, and 21were carried to term, with 18 subjects delivering live infants without complications (1 pair of twins). One subject delivered an infant with meconium aspiration pneumonia (MedDRA preferred term = congenital pneumonia). Two subjects who received 150 mg elagolix QD in Phase 2 endometriosis studies delivered infants with congenital anomalies: 1 infant with tracheoesophageal fistula with findings of patent ductus arteriosus, tricuspid valve incompetence, and pneumothorax and 1 infant with cleft soft palate. Internal and external causality assessment of these malformations supported that both congenital malformation cases were unlikely to be related to elagolix.

In Phase 3 studies in endometriosis 14 pregnancies have been reported in Study M12-665 and 6 have been reported in Study M12-671. In the aforementioned Phase 2b UF study, 1 on-treatment pregnancy has been reported.

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. Women are also counseled on the unknown, thus potential, risk to children born to mothers exposed to elagolix during pregnancy, including the possibility of malformations.

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.

Efficacy in Phase 2 Uterine Fibroid Studies

The main objectives of the uterine fibroids Phase 2 program in premenopausal women were as follows: 1) to select the most appropriate dose(s) of elagolix to evaluate in Phase 2b and Phase 3 from both an efficacy and safety perspective, and 2) to assess the need for, adequacy, and type of add-back therapy to be used in conjunction with elagolix. The first objective was accomplished in the 3-month Phase 2a, dose-ranging POC study, Study M12-663, and the second objective was accomplished in both Phase 2 studies (need for and type of add-back in Phase 2a and adequacy of add-back therapy in Phase 2b [6-month safety and efficacy study]).

The Phase 2a dose-finding, POC study evaluated TDDs of elagolix of 200, 400, and 600 mg in premenopausal women with HMB associated with uterine fibroids. While it was anticipated that some women would likely benefit (reduction in menstrual bleeding), even with low doses (TDD of 200 mg) of elagolix, the agreed-upon dose selection criteria for Phase 2b was predicated on a dose in Phase 2a that provided the most robust response (responder rates of approximately > 80% for the composite bleeding assessment) and an acceptable safety and bleeding profile for the majority of women. It was known that to support long-term dosing with elagolix at these higher doses, hormone add back therapy would be required for all of these.

All elagolix doses resulted in statistically superior reductions in the mean percentage of menstrual blood loss (MBL) from baseline measured by the alkaline hematin method compared to placebo, with the largest effect noted with the 300 mg BID dosing regimen. With regard to the primary endpoint, the add-back therapy with low-dose E2/NETA or cyclical EP had marginal effects on the efficacy of elagolix. Furthermore, co administration of low-dose E2/NETA or cyclical EP (progesterone administered from Day 17 through Day 28 per treatment cycle) had comparable efficacy on the percentage change in MBL or the percentage of subjects who met the composite bleeding endpoint (MBL volume of < 80 mL at the Final Month [last 28 days of treatment], ***and*** ≥ 50% reduction in MBL volume from Baseline to the Final Month [last 28 days of treatment]) relative to elagolix administration alone. When co-administered with elagolix (200 or 300 mg BID), both add-back therapy regimens were efficacious in reducing the percentage of moderate-to-severe bleeding days, with increases in bleeding days being primarily due to spotting.

Based on data from the Phase 2a study, a TDD of 600 mg and 2 doses of E2/NETA add-back therapy (low-dose E2/NETA and standard-dose E2/NETA) were selected for Phase 2b.

The Phase 2b study evaluated the safety and efficacy of elagolix TDD of 600 mg administered either (QD or BID regimens), alone and in combination with 2 different strengths of E2/NETA in premenopausal women age 18 to 51 years with HMB associated with uterine fibroids. The study consisted of an approximate 2.5- to 3.5-month Screening Period, a 6-month Treatment Period, and a 6-month Post-Treatment Follow-Up Period. Cohort 1 utilized elagolix 300 mg BID dosing (with and without add-back therapy) while Cohort 2 utilized elagolix 600 mg QD dosing (with and without add-back therapy).

The primary efficacy endpoint was the percentage of subjects meeting a composite endpoint consisting of 2 bleeding assessments: MBL volume of < 80 mL at the Final Month (last 28 days of treatment), ***and*** ≥ 50% reduction in MBL volume from Baseline to the Final Month (last 28 days of treatment). The key secondary efficacy endpoints include change in fibroid and uterine volume by ultrasound (and MRI in a subset), other

key bleeding assessments, specific non-bleeding assessments based on a Non-Bleeding Symptoms Uterine Fibroid Questionnaire (NBUFSQ), and other QOL variables including UFS-QOL. The safety and tolerability objectives include the assessment of standard safety parameters, in addition to hypoestrogenic adverse events of interest, including BMD loss as assessed by dual energy x-ray absorptiometry (DXA) and vasomotor symptoms, such as hot flush. Endometrial health via transvaginal ultrasound (TVU) and endometrial biopsy are also evaluated.

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

- Robust efficacy in controlling HMB (composite bleeding endpoint of 91.9%, 85.5%, and 79% in the elagolix 300 mg BID alone, elagolix 300 mg BID plus low-dose E2/NETA, and elagolix 300 mg BID plus standard-dose E2/NETA treatment groups, respectively) associated with uterine fibroids
- 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.

Overall, preliminary findings 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.

Preliminary 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 either strength of E2/NETA) met the primary endpoint, which is the proportion of subjects who achieved an 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.

AbbVie Ongoing Phase 3 Clinical Studies

Endometriosis

The Phase 3 endometriosis clinical development program is comprised of two 6-month replicate, randomized, double-blind, placebo-controlled pivotal studies (Studies M12-665 and M12-671), each with complimentary 6-month safety/efficacy extension studies (Studies M12-667 and M12-821). The extension studies are ongoing. The primary objective of the pivotal studies are to evaluate the safety, tolerability, and efficacy, of elagolix, administered QD or BID compared to placebo, in the management of moderate to severe endometriosis-associated pain while taking into account the use of rescue analgesics. Secondary efficacy objectives include assessments of other endometriosis-related symptoms, analgesic use, as well as quality of life (QoL) endpoints. The 6-month extension studies assess the long-term safety and efficacy of elagolix for a total treatment duration of up to 12 months.

Phase 3 Clinical Development Program for Uterine Fibroids

The overall objective of the 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. Furthermore, the goal is to generate data that supports long-term use with this treatment regimen.

The primary objective of these pivotal studies is to evaluate the efficacy and safety of elagolix 300 mg BID in combination with add-back therapy (E2/NETA) as compared to placebo to reduce HMB associated with uterine fibroids. Given the difficulties with extending placebo for periods beyond 6 months, the elagolix 300 mg BID alone arm serves as a reference arm, which will be useful in fully understanding the protective effects of standard dose E2/NETA on BMD over a 12-month treatment period.

Subjects who complete either pivotal study (Studies M12-815 or M12-817) will have the option to enter into the extension study (Study M12-816) to receive an additional 6 months of therapy, for a total of up to 12 months of active treatment for those randomized in the pivotal studies to active treatment and a total of 6 months of treatment for those randomized to placebo in the pivotal studies.

Subjects who discontinue or complete treatment in either pivotal study and choose not to participate in or are ineligible for entry into the extension study will enter into the 12-month Post-Treatment Follow-Up Period of their respective study.

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.

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.

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 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, and/or semi-invasive procedures as a chronic pharmacologic treatment for HMB 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 further defined in this Phase 3 trial.

4.0 Study Objective

The objectives of this study are to:

- Assess the efficacy, safety and tolerability of elagolix 300 mg BID in combination with E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg QD), versus placebo to reduce HMB associated with uterine fibroids in premenopausal women 18 to 51 years of age.
- The study will also characterize the impact of E2/NETA on the safety/tolerability (including BMD and other hypoestrogenic side effects) and efficacy of elagolix.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This Phase 3, randomized, double-blind, multicenter, placebo-controlled study is designed to evaluate the efficacy, safety and tolerability of elagolix alone and in combination with E2/NETA in the management of premenopausal women with HMB associated with uterine fibroids. Approximately 400 subjects will be randomized in a 1:1:2 ratio to 1 of the following 3 treatment groups:

- placebo (n = 100)
- elagolix 300 mg BID (n = 100)
- elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) QD (n = 200)

This study is designed to enroll approximately 400 subjects across approximately 125 clinical study sites to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. If the target number of enrolled subjects has been met, there is a possibility that additional subjects in screening will not be enrolled.

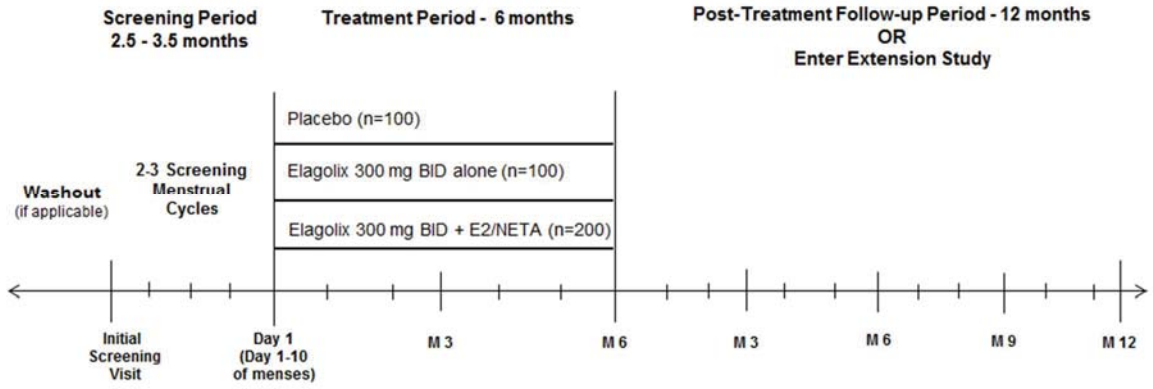
The study consists of 4 periods as follows:

1. Washout Period prior to Screening (if applicable)

2. Screening Period of approximately 2.5 to 3.5 months prior to first dose of study drug
3. 6-month Treatment Period
4. 12-month Post-Treatment Follow-Up Period (OR Subjects may enter an extension study [Study M12-816] if they are willing and qualify, based on safety parameters, to receive an additional 6 months of treatment, followed by 12 months of follow-up).

Subjects will visit the site for assessments and testing during the Washout Period, if applicable, during the Screening Period (Initial Screening Visit, Screening Product Collection Visits [PCVs] for assessment of menstrual blood loss) and Treatment Period (Day 1 [Randomization] and monthly during Month 1 through Month 6). Following the 6-month Treatment Period, subjects will enter into a 12-month Post-Treatment Follow-Up Period or an extension study. The Study Periods are illustrated in Figure 1.

Figure 1. Study Schematic



Washout Period

Following informed consent, subjects, who are taking or were taking exclusionary medications such as hormonal medications or antifibrinolytics, prior to screening that require washout, must enter a Washout Period. Subjects must complete the Washout

Period and have had at least 1 menses after completion of washout, prior to entering the Screening Period. The duration of the required washout period is based on the excluded medication that the subject is currently taking, or was taking. The requirements for washout are provided in detail in Section 5.2.3.1, Prior Hormonal/Anti-Hormonal Medications and the assessments to be performed are specified in Appendix C, Study Activities.

A pelvic ultrasound (transabdominal [TAU] and transvaginal [TVU]) may be performed after informed consent is obtained 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 the subject unnecessarily undergoing a lengthy washout of hormonal medications. Subjects will begin the use of non-hormonal dual contraception and receive counseling on the importance of consistent, appropriate and effective use of birth control.

Screening Period

Subjects who do not require washout will enter directly into the approximate 2.5- to 3.5-month Screening Period and will provide written informed consent before any study-related procedures are performed. Subjects will undergo screening procedures (e.g., safety labs, pelvic ultrasound [TAU/TVU], DXA) as specified in Appendix C, Study Activities, to establish eligibility based on inclusion and exclusion criteria.

Subjects will be required to use dual non-hormonal contraception and will receive counseling on the importance of consistent, appropriate and effective use of birth control throughout the Screening Period.

A pelvic ultrasound (TAU and TVU) will be performed, 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; in addition to the ultrasound, 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; however, have SIS images which are unable to fully assess the endometrial cavity, may undergo additional imaging modalities such as MRI for further evaluation in Screening.

Eligibility based on MBL (> 80 mL for each of 2 menstrual cycles) will be established using the alkaline hematin method. Sanitary products and sanitary product collection kits will be dispensed during screening and training will be provided 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 screen fail may be re-screened on a case-by-case basis after consulting the AbbVie TA MD for 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 visit.

There may be an option for subjects to have a Product Collection Visit conducted at home by a Home Health Care Agent who will go to the Subject's home to draw a venous blood sample and retrieve the collection keg to return to the site.

Treatment Period

The Treatment Period begins with Day 1, which will occur between 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 randomized to receive either placebo (n = 100), elagolix 300 mg BID (n = 100) or elagolix 300 mg BID plus E2/NETA QD (n = 200). The first dose of study drug will be administered at the study site on Day 1. Subjects will be instructed to self-administer study medication or matching placebo twice daily (in the morning and in the evening approximately 12 hours apart) orally without regard to food throughout the 6-Month Treatment Period. Subjects randomized into the study will visit the site during the 6-Month Treatment Period on Day 1, and then monthly (28-day intervals) from Month 1 through Month 6. Additional study visits may occur, either for subjects returning their sanitary products for analysis of alkaline hematin at a Product Collection Visit or for a Premature Discontinuation Visit (if applicable).

Pregnancy (urine and/or serum) tests will be performed at each visit throughout the study and subjects will be counseled at each visit on appropriate and effective forms of dual non-hormonal contraception to promote pregnancy prevention.

Sanitary product collection kits will continue to be dispensed at all Treatment Period visits. Subjects will be required to collect all sanitary products on days with menstrual bleeding or spotting throughout the Treatment Period. Subjects will return sanitary products to the clinical study site, either during a scheduled monthly visit or at a Product Collection Visit. As in Screening, there may be an option for subjects to have a Product Collection Visit conducted at home by a Home Health Care Agent.

If a Subject does not return a sanitary product collection keg at any site visit (scheduled monthly visit, Product Collection Visit or Unscheduled Visit) during the Treatment Period, the Uterine Bleeding Questionnaire (UBQ) will be administered by the Site Staff to indicate if the subject had any bleeding or spotting since the last study visit. If the subject had bleeding or spotting, she will be asked why she did not return a sanitary product collection keg. The subject's responses will be recorded on the UBQ by the Site Staff.

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

An MRI will be performed at Day 1, unless performed during Screening, and at subsequent time points as outlined in Appendix C for subjects who consent to participate in the MRI subset.

Subjects will continue the use of dual non-hormonal contraception and receive counseling on the importance of consistent, appropriate and effective use of birth control. Subjects who prematurely discontinue from the Treatment Period will be asked to complete Premature Discontinuation procedures and enter the Post-Treatment Follow-Up Period. Premature Discontinuation Procedures will be performed as specified in Appendix C, Study Activities.

Eligible subjects who complete the 6-month Treatment Period, qualify and provide informed consent will be allowed to participate in a 6-month extension study in which all subjects will receive active treatment with either elagolix 300 mg BID alone or elagolix 300 mg BID plus E2/NETA. All activities for these subjects are outlined in the extension study protocol (Study M12-816). The Month 6 Treatment Visit in this study may be conducted over several days to allow for eligibility to be confirmed prior to participation in the extension study.

Post-Treatment Follow-Up Period

For subjects entering the 12-month Post-Treatment Follow-Up Period, visits will occur either by phone or on-site from Months 1 through 12.

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 and will remind subjects of the importance of consistent use of appropriate and effective dual non-hormonal contraception throughout the Post-Treatment Follow-Up Period. Subjects may begin taking hormonal contraceptive preparations only after completing the Post-Treatment Follow-Up Month 2 Visit and having returned sanitary products for a full menses (menses with full menstrual flow) in the Post-Treatment Follow-up Period. If the subject's full menses has not returned by the Post-Treatment Follow-Up Month 2 Visit, an adverse event of amenorrhea should be documented.

During the on-site visits, Post-Treatment Month 1, 3, 6, 9 and 12, procedures will be performed as specified in Appendix C, Study Activities.

Subjects will be required to collect sanitary products for their first menses with full menstrual flow in the Post-Treatment Follow-up Period. If the subject misses collecting sanitary products for her first full menses, she will be required to collect sanitary products for her next full menses. Subjects will return the sanitary products at a Product Collection Visit within approximately 5 days after cessation of bleeding or spotting. The Post-Treatment UBQ will be administered by Site Staff at each Phone or Site Visit until the subject has returned sanitary products from one full menses in the Post-Treatment Follow-up Period. Once a subject returns sanitary products from a full menses in the Post-Treatment Follow-up Period, the Post-Treatment UBQ no longer needs to be completed.

Subjects who prematurely discontinued from the Treatment Period prior to the Month 3 Study Visit, (e.g., subjects who received < 3 months of study drug), will enter into the Post-Treatment Follow-Up Period, however, the number of procedures/assessments performed in the Post-Treatment Period will be reduced and these subjects will complete

the study at the Post-Treatment Follow-up Month 6 visit (unless the reason for premature discontinuation was due to BMD decrease or an adverse event of fracture). Procedures/assessments should be performed as specified in Appendix C, Study Activities.

Unscheduled Visit and Unscheduled Visits for Delays in Roll-Over

In the event an Unscheduled Visit is necessary during the Treatment or Post-Treatment Follow-Up Period, the site will perform at minimum, the UBQ and an assessment of adverse events and concomitant medications. Unscheduled visits should be limited to when a subject is required to return to the office or off-site facility to repeat a procedure or to conduct a procedure to assess safety and the visit is not occurring at the same time when other study related-procedures are scheduled to occur. For unscheduled visits when study drug is dispensed (e.g., to replenish lost or damaged study drug), the subject will also be required to have a negative urine pregnancy test result prior to dispensing. Clinical judgment should dictate when other safety assessments (such as vital signs and/or symptom-directed physical examination) should be conducted and should also support the reason for the unscheduled visit.

Subjects awaiting test results to determine eligibility into the extension study may be required to remain in the Treatment Period to receive additional study drug until results become available. Visits associated with this waiting period will be documented as Unscheduled Visits and subjects will continue to undergo study-related assessments and procedures as outlined in Appendix C and Section 5.4.4 Delays in Rollover into the Extension Study.

Visit Windows

Visit windows will be allowed for the monthly visits during the Treatment and Post-Treatment Follow-Up Periods. Each subsequent monthly visit should be scheduled based on the date of the Day 1 (Randomization) visit. At the Month 6 Treatment Period Visit, a –4 or +6 day visit window will be allowed in order to collect sanitary products from the last episode of menstrual bleeding or spotting prior to the Month 6 visit if

menstrual bleeding starts immediately prior to or coincides with the scheduled visit. The subject will be instructed to continue taking study drug from the extra blister card until she returns for the Month 6 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 Period: Months 1 – 5	±4 days
Treatment Period: Month 6	–4 or +6 days
Post-Treatment Follow-Up Period: Months 1 – 12	±7 days
Assessment-Specific Windows for Treatment and Post-Treatment Period	
Study Visit/Assessment	**Visit Windows**
Treatment Period	
Day 1: Ultrasound	±7 days
Day 1: MRI (if participating in MRI subset)	±7 days (unless an MRI was required in Screening. If MRI required in Screening, the Day 1 MRI will not be performed)
Month 3: Ultrasound	±7 days
Month 6: Ultrasound, MRI (if participating in MRI subset) DXA Scan and endometrial biopsy	–15 or + 4 days
Post Treatment Follow-Up Period	
Month 3: Ultrasound, MRI (if participating in MRI subset)	–15 or +4 days
Month 6: Ultrasound, DXA Scan	–15 or +4 days
Month 12: DXA Scan	–15 or +4 days

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

5.2 Selection of Study Population

Premenopausal female subjects (aged 18 to 51 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 Medical Director (TA MD) listed in Section 6.1.5 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 washout (if applicable), or initiation of any screening or study-specific procedures.
2. Subject is a premenopausal female 18 to 51 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 fibroid present meets at least one of the following criteria:
   - Intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter)
   - Subserosal fibroid ≥ 4 cm
   - 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 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.
7. Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Washout (if applicable), Screening, Treatment and Post-Treatment Periods (Subject may start hormonal contraception after completion of the Post-Treatment Month 2 Visit provided her menses has returned). 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 (including ligation and blockage methods such as Essure®), 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.
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. (prognostic and predictive)
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. (prognostic and risk)
8 – 9	These are standard criteria to ensure general good health and the safety of the subjects. (risk)
10, 11	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications. (predictive and risk)

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 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 ultrasound shows a simple ovarian cyst > 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 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 or country 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 < 8 g/dL (subjects with initial screening hemoglobin results < 8 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 moderate to severe hepatic impairment (including aspartate aminotransferase (ASAT/SGOT) or alanine aminotransferase (ALAT/SGPT) 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 or ECG with QT interval corrected for heart rate (QTc) > 450 msec at Screening using either Fridericia's correction (QTcF) or Bazett's correction (QTcB).

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 24 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 1.5 or more standard deviations below normal (T-score ≤ –1.5)
    - 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).
    - Presence of a condition that is associated with a decrease in BMD (e.g., uncontrolled hyperthyroidism, uncontrolled hyperparathyroidism, anorexia nervosa)
    - History of low-trauma bone fractures (e.g., fracture resulting from a fall from a standing height or lower)
    - History of 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

17. Subject has a history of major depression or post-traumatic stress disorder (PTSD) 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) at Screening or Day 1, prior to randomization.

19. Subject has a clinically significant medical condition that requires intervention **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 a history of clinically significant condition(s) or documented history of a severe, life-threatening or other significant sensitivity to any drug.

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 cannot tolerate estrogen- or estrogen plus progestin-containing preparations (e.g., oral contraceptives), or these preparations are contraindicated due to medical reasons.

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

27. 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 after completion of washout for LNG-IUS or after removal of the CU-IUD, the subject can be screened for eligibility to be considered for randomization.

28. 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 injectable (for occasional use) corticosteroids are allowed.

29. Subject is using oral retinoid preparations such as Accutane® (isotretinoin). Topical isotretinoin applications are permitted.

30. Subject has a history of drug abuse and/or alcohol abuse within 12 months prior to Screening.

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

32. 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.

33. 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.

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. (prognostic and predictive)
5 – 13, 15 – 23, 29, 30	These are standard criteria to ensure general good health and the safety of the subjects. (prognostic and risk)
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. (risk)
31, 32	This criterion was selected to avoid bias for the evaluation of efficacy and safety by prior participation in an elagolix study. (predictive and risk)
25 – 28	These criteria were selected to ensure that efficacy can be adequately assessed. (predictive and risk)
33	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. (predictive)

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 electronic case report forms (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 Therapeutic Area Medical Director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapy.

5.2.3.1 Prior Hormonal/Anti-Hormonal Medications

Subjects using or who have used hormonal contraception or other hormonal/anti-hormonal therapies may be considered for study participation provided they complete the required washout. Subjects must also return to 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. Subjects must also return to 1 menses after completion of Washout before the Screening Period can begin. Discontinuation of hormonal contraception should be done according to prescribing information (e.g., complete current cycle of birth control pills).

The minimum washout intervals for hormonal medications (including LNG-IUS) prior to Screening are described in Table 2. Subjects entering washout will be required to undergo study specific procedures, as outlined in Appendix C, Study Activities. Subjects may enter the Screening Period provided they have returned to 1 menses after the required washout period has been completed. Subjects who have a CU-IUD and agree to have the CU-IUD removed may enter screening, however the subject must return to 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.

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)	90 days from injection	1 menses
GnRH antagonist	90 days	
Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate, Vilaprisan)		
Nafarelin acetate		
Danazol (Cyclomen®)		
Aromatase inhibitors		
Oral contraceptives	30 days	
Oral, transdermal or intravaginal estrogen preparations*		
Oral, intravaginal or transdermal progesterone/progestin preparations, including tibolone*		
Synarel® (Nasal Spray)		
Progesterone and LNG-IUS, sub-dermal progestin implant (e.g., Nexplanone®), GnRH agonist – 1 month depot Exception: levonorgestrel 1.5 mg or ulipristal acetate 30 mg used for emergency contraception	30 days after removal or injection	
Lupron Depot® 3.75 mg		
NuvaRing®		
Antifibrinolytics	2 weeks	

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

** 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.

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.

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 < 8 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, Treatment and Post-Treatment Follow-Up Periods, however inhaled

corticosteroids for the treatment of asthma are permitted. Over-the-counter and prescription topical, inhaled, intranasal or 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 Period and until the Post-Treatment Follow-Up Month 2 Visit and return to menses. If the Subject has not returned to menses, she must continue the use of dual non-hormonal contraception.

For subjects who are prescribed/administered the emergency contraceptive pill during the study, the AbbVie TA MD must be informed.

Tranexamic acid should not be taken during the Screening, Treatment or Post-Treatment Follow-Up Period, however tranexamic acid, if necessary, can be prescribed following completion of the Post-Treatment Follow-up Month 2 visit and the subject has returned to first full menses.

Due to the extensive list of herbal remedies and supplements, please contact the AbbVie TA MD for any that may be prohibited. Generally-speaking, 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, Treatment and Post-Treatment Follow-Up Period.

Table 3. Prohibited Medications

Prohibited During the Washout, Screening, Treatment and Post-Treatment Follow-Up Periods	
Hormonal/Anti-Hormonal Medications[%], such as:	GnRH agonists leuprolide acetate (Lupron®), nafarelin acetate (Synarel®), goserlin acetate (Zoladex®) GnRH antagonists (other than elagolix) Danazol (Danocrine®) 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) 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®) Aromatase Inhibitors (e.g., Anastrozole [Arimidex®], Exemestane [Aromasin®])
Non-hormonal estrogen supplements[#]	Natural Estrogen preparations (e.g., soy-containing supplements, black cohosh)
Antifibrinolytics[%]	Tranexamic acid (Lysteda, Cyklokapron, Cyclo-f)

Table 3. Prohibited Medications (Continued)

Prohibited During the Washout, Screening, Treatment and Post-Treatment Follow-Up Periods	
Moderate or strong CYP3A Inducers,[9] 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
Bisphosphonates, RANKL inhibitors, Anabolic Bone Agents or rPTH, such as:	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
Oral Retinoids (topical applications are permitted), such as:	Accutane® (isotretinoin)

* 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 Post-Treatment Follow-up Month 2 Visit and return to menses. Tranexamic acid, if necessary can be prescribed following completion of the Post-Treatment Follow-up Month 2 visit 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 in Section 6.1.5 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 (hormonal medication taken after completion of the Post-Treatment Follow-Up Month 2 Visit and return to menses), 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 and Pregnancy Testing

Contraception Counseling/Dispense Contraceptives

Investigators and Study Coordinators 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 at every visit throughout their participation in the study on the importance of pregnancy prevention and the use of appropriate and effective methods of birth control during the Washout Period, if applicable, during the Screening, Treatment, and Post-Treatment Follow-Up Periods of the study.

Subjects must agree to use two forms of non-hormonal contraception (dual contraception) consistently throughout the Washout (if applicable), Screening and Treatment Periods and Post-Treatment Follow-Up Periods (Subjects may begin the use of hormonal contraception (e.g., oral or IUD) after completing the Post-Treatment Follow-up Month 2 Visit and after return to first full menses in the Post-Treatment Follow-up Period).

Subjects using an LNG-IUS, who agree to have the LNG-IUS removed must complete washout per Section 5.2.3.1, and return to 1 menses after completion of washout prior to Screening. Subjects using a CU-IUD, who agree to have the IUD removed may enter screening, however the subject must return to 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.

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 occlusion (including ligation and blockage methods such as Essure®) 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 indicated above.

Subjects may begin the use of hormonal contraception in place of dual non-hormonal contraception during the Post-Treatment Follow-up Period if they meet both of the following:

- Completed the Post-Treatment Follow-up Month 2 Visit
- Returned to first full menses in the Post-Treatment Follow-up Period

If subject does not return to full menses she must continue use of dual non-hormonal contraception.

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 her full awareness that the potential risks of study drug (elagolix) 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 dual non-hormonal contraception throughout her study participation (during the

Washout Period, if applicable, Screening, Treatment and Post-Treatment Follow-Up Period.

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 cyclicity, and that fetal abnormalities have been observed in women who have received elagolix in clinical studies that were not deemed to be related to elagolix based on the totality of data; 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 sites with a supply of materials to promote pregnancy prevention, including contraceptives (condoms and spermicides), and lubricants 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 a contraception method of their choice from the contraceptives provided by the Sponsor and practice the allowable methods of dual contraception. The site will assess the subject's basic understanding of the proper use through discussion and demonstration of proper techniques, including proper diaphragm use.
    - The site will dispense contraceptives to subjects throughout Washout, if applicable, Screening, Treatment, and through the Post-Treatment Follow-Up, as needed. Subjects may begin the use of hormonal medication after completion of the Post Treatment Follow-up Month 2 visit and return to first full menses.
    - The source documents will capture date contraception counseling was performed, whether the subject is sexually active with men, the type of contraceptive used, a change in contraceptive method, use of a non-study

supply brand, contraceptives provided to the subject, and the date supplies were provided.

- As appropriate, the subject will be asked to attest by signature at the time of consent, and in a stand-alone attestation form at Day 1 and at the Month 6 or Premature Discontinuation study visit that allowable methods of contraception, as described during the pregnancy prevention counseling, are being practiced.
- For subjects who have had a bilateral tubal occlusion, attestation is only required to be collected once at the time of consent.

4. Subjects will be reminded to use dual non-hormonal contraception.
5. The study drug will be dispensed as a monthly supply at the beginning of each month during the Treatment Period to promote frequent interaction with site staff and opportunities for continued education.
6. At each visit, subjects will be asked to name the type of contraception used since their last visit and will be reminded of the proper use of that type of method to prevent ineffective contraception and the risk of unexpected pregnancy due to unprotected sexual activity.

Pregnancy Tests and Reporting a Pregnancy

Urine and/or serum pregnancy tests will be performed as specified in Appendix C, in all subjects regardless of sexual activity status or method of contraception. The subject must have a confirmed negative urine pregnancy test within 24 hours prior to performing the SIS and endometrial biopsy procedures.

The urine pregnancy test result on Day 1 must be reviewed and determined to be negative prior to randomization. In addition, during the Treatment Period, the urine pregnancy test must be negative prior to providing subjects with their next monthly supply of study drug, (including an unscheduled visit at which study drug is dispensed).

Home pregnancy test kits will be provided to the subject at the Initial Screening Visit and Month 6 or Premature Discontinuation visit during the Treatment Period if logistically, a

urine pregnancy test cannot be performed at the study site or other medical facility within 24 hours prior to an SIS and/or endometrial biopsy. The subject must self-administer and report a negative urine pregnancy test result to the site within 24 hours prior to undergoing these procedures.

A positive urine pregnancy test result 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.

An ultrasound examination will be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery if the subject becomes pregnant during the Treatment or Post-Treatment Follow-Up Periods of the study. 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 infant births.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Pharmacogenetic 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 the monitoring of study drug accountability (Section 5.5.7) and the collection of concomitant medication and adverse event information (Section 5.2.3 and

Section 6.1., respectively). Study data will be recorded in source documents and on eCRFs.

The Screening Period will occur within approximately 2.5 to 3.5 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, 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 may be performed within the visit windows specified in Table 1. Scheduled monthly visits during the Treatment and Post-Treatment Follow-Up Period are based on a 28-day month.

It is recommended that the pelvic ultrasound, MRI (if applicable), DXA scan and endometrial biopsy for the Month 6 Visit be conducted within approximately 15 days prior to the scheduled Month 6 Visit to ensure the images are received and acceptable for review by the central vendor. If eligibility into the extension study cannot be determined at the pivotal study Month 6 visit, an additional study drug kit will be dispensed to the subject at the Month 6 Visit. Refer to Section 5.4.4, Delays in Roll-Over for the Extension Study for further instructions.

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

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. Pharmacogenetic (PG) testing is optional and a subject must be provided a separate informed consent form for this blood collection. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Screen Failures and Re-Screening of Subjects

Subjects who have signed 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 endometrial biopsy) or did not meet all entry criteria will be considered Screen Failures. The reason(s) for screen failure will be recorded in the source documents and will be captured in the eCRF. Subjects who screen fail may be re-screened on a case-by-case basis after consulting the AbbVie TA MD for approval.

Medical/Social History

The following information will be collected after signing the informed consent, either during the Washout Period (if applicable) or during the Screening Period for those subjects who do not require washout.

- Complete medical history, including documentation of any clinically significant medical conditions and medications
- History of tobacco and alcohol use

The medical history will be reviewed and updated prior to dosing on Study Day 1 (Randomization) 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:

Detailed gynecological/uterine fibroid history, including:

- 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:
    - Number of pregnancies
        - Number of live birth term pregnancies
        - Number of live birth pre-term pregnancies
    - 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 updated prior to dosing on Study Day 1 (Randomization) and will serve as the baseline for clinical assessment.

Gynecological (Pelvic and Breast) Examination

A complete breast, and pelvic examination, including external genitalia will be performed during the Screening Period and at the Month 6 or Premature Discontinuation visit in the Treatment Period. A screening breast examination may be omitted, based on local or country guidelines, e.g., breast examinations are routinely or only conducted by breast specialists. In these cases, source documentation should indicate reason not performed.

Pap Test

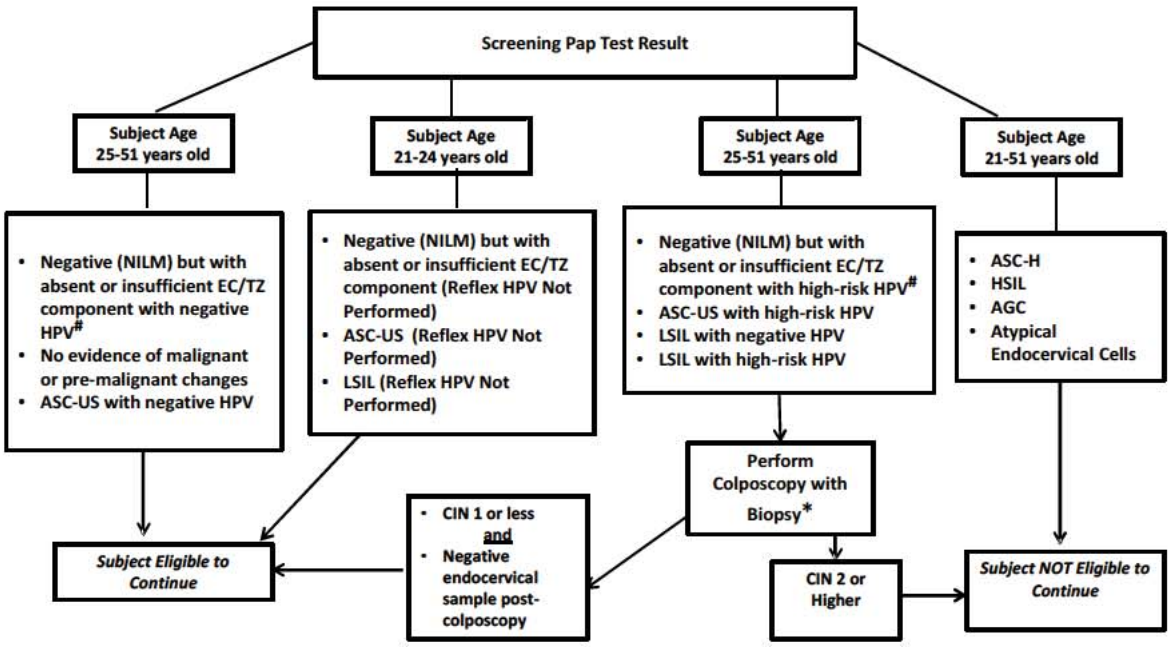
A Pap test will be performed in subjects ≥ 21 years of age during the Screening Period, using the Thin Prep® Pap Test™ provided and analyzed by the central laboratory. If the subject is experiencing menstrual bleeding that precludes the performance of the Pap test, this procedure should be performed 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.

Figure 2. Pap Test Eligibility



*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

Reflex performed only if subject is > 30 years of age

Endometrial Biopsy

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 Lab 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. Misoprostol for cervical dilatation is allowable. An office hysteroscopy may be performed to obtain the endometrial biopsy sample if the endometrial biopsy cannot be performed because of anatomical reasons.

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

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 must be obtained before the subject can be randomized. 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 AbbVie TA MD must be contacted to obtain approval to perform a repeat biopsy. The repeat biopsy must meet eligibility criteria prior to Study Day 1 (Randomization).

During the Treatment Period, an endometrial biopsy will be performed at Month 6 visit or at the Premature Discontinuation visit (if subject prematurely discontinues after the

Month 3 Visit). It is recommended that the biopsy for the Month 6 Visit is performed approximately 15 days prior to the scheduled Month 6 visit to ensure the results are received from the central laboratory in order to determine eligibility for inclusion into the extension study. If biopsy results are not available by the Month 6 visit of the Treatment Period, refer to Section 5.4.4 for instructions on assigning additional study drug kits for delays in roll-over until eligibility is determined.

If the Month 6 biopsy results are normal or the sample contains scant endometrium without abnormalities, the subject is eligible to enter the extension study.

In the event the Month 6 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. If upon repeat, a sample cannot be obtained or remains insufficient, the AbbVie TA MD should be consulted.

If a repeat biopsy is performed and the results are normal or the sample contains scant endometrium without abnormalities, the subject is eligible to enter the extension study.

Subjects with abnormal endometrial pathology results (including, endometrial hyperplasia with or without atypia and endometrial cancer) at Treatment Month 6 are not eligible to enter the extension study and instead will enter the Post-Treatment Follow-up Period. The endometrial pathology should be managed according to standard of care.

Physical Examination

A complete physical examination will be performed during the Washout Period (if applicable) or Screening Period and will include height and weight measurements (the subject should not wear shoes). Subjects who entered washout will only be required to have a symptom-directed physical examination performed when they enter the Screening Period.

During the Treatment Period and Post-Treatment Follow-Up Periods, a complete physical examination will be performed at Day 1 (prior to dosing), Month 6 and Post-Treatment Follow-up Month 6 or Premature Discontinuation. The complete physical examination at Day 1, Month 6 or Premature Discontinuation will include weight measurements. Symptom Directed Physical Examinations will be performed as specified in Appendix C.

Clinically significant physical examination findings prior to randomization will be recorded as medical history. Any clinically significant physical examination findings after dosing will be recorded in the source documents and in the eCRFs as adverse events.

Vital Signs

Vital sign determination of heart rate, blood pressure, respiratory rate and body temperature will be obtained at all visits during the study as indicated in Appendix C. The blood pressure and heart rate measurements should be taken prior to scheduled blood collections. Body temperature measurements should be assessed using the same modality consistently throughout the study, e.g., oral, aural, axillary, etc., and the modality will be reported in the source documents and eCRF.

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

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be conducted during the Screening Period and at the Treatment Month 6 Visit or Premature Discontinuation visit (if applicable) of the Treatment Period, as indicated in Appendix C.

For any abnormal screening test results, the ECG may be repeated at a later date, however, the subject must meet eligibility prior to Study Day 1 (Randomization). Final results will be entered into the eCRF.

The Investigator or qualified designee at the study site will determine if any findings outside the normal physiological variation 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. For ECG with QT interval corrected for heart rate (QTc) > 450 msec, the correction formula used (i.e., Bazett's or Fridericia's) should be recorded in source documents and the eCRF. The study site should use the same correction formula consistently throughout the study.

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. Local mammogram results and final interpretation must be entered into the eCRF.

If a subject's mammogram results are incomplete (BI-RADS 0) and needs 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 the study.

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 randomization. Any further imaging or testing will be performed outside of the protocol and should follow standard of care. Subjects may be re-screened on a case by case basis after review of the results and consulting the AbbVie TA MD for approval.

The local radiologist's interpretation will be used to determine if a subject meets eligibility. Subjects with normal or benign findings or BI-RADS Classifications 1, 2 or 3 as outlined in Appendix D will be eligible for randomization. Subjects with an abnormal mammogram or BI-RADS 0, 4 or 5, will not be eligible for randomization into the study.

Subjects should continue with recommended mammography screening outside of the protocol per local guidelines and standard of care during the study.

Central Imaging Procedures

Fibroid and uterine assessments will be obtained using pelvic ultrasound (TAU and TVU) throughout the study, and SIS at Screening. In addition to the TAU and TVU, an MRI will be performed in a subset of subjects during the Treatment and Post-Treatment Follow-up Period who consent to participate in the MRI Subset. The goal of the MRI subset is to evaluate uterine fibroid size and volume and uterine volume using another technique in addition to ultrasound. All ultrasound and MRI images will be sent to the Central Imaging Core Lab (ICL) for review to determine eligibility for randomization and to monitor safety during the Treatment and Post Treatment Follow-Up Periods.

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 ICL. Images should be sent/transmitted to the ICL 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 ICL.

The pelvic ultrasound (TAU, TVU and SIS) and MRI (if applicable) will be assessed both locally and by the ICL. The ICL 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 ICL 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 AbbVie 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 make any eligibility and 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 and SIS images will not be recorded in the eCRF.

The ICL will only issue a report for pelvic ultrasound at Treatment Month 6. A report for all other Treatment and Post-Treatment timepoints for pelvic ultrasound and MRI will only be issued if any significant changes are observed that may affect subject safety during the study. In these cases, the Investigator should review the local ultrasound and/or MRI images and treat as per standard of care.

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

It is recommended that the pelvic ultrasound and MRI (if applicable) performed for the Month 6 Visit are conducted approximately 15 days prior to the scheduled Month 6 Visit to ensure the images are received and acceptable for review by the central vendor. The central pelvic ultrasound report is only required prior to rollover in the event the Month 6 endometrial biopsy cannot be performed or biopsy results are insufficient. In this case the central pelvic ultrasound is required to determine if the endometrial thickness is ≥ 4 mm in which case the subject needs a repeat biopsy prior to rollover (see Section 5.3.1.1 Endometrial Biopsy). If the results are not available by the Month 6 visit of the Treatment Period to determine need for a repeat endometrial biopsy, refer to Section 5.4.4 for instructions until results are available to determine eligibility into the extension study.

Qualifying Uterine Fibroids:

The following types of uterine fibroids will qualify a subject for randomization:

Fibroid size/uterine volume:

- At least 1 fibroid with a diameter ≥ 2 cm (longest diameter)

OR

- Multiple fibroids with a total uterine volume of ≥ 200 cm^3 to $\leq 2{,}500$ cm^3 as documented by centrally read imaging vendor

Type of fibroid/fibroid location:

- Intramural fibroids
- Submucosal non-pedunculated fibroids
- Large (≥ 4 cm) subserosal fibroid

The following types of uterine fibroids are exclusionary:

- Intracavitary pedunculated submucosal fibroids
- Solitary pedunculated subserosal fibroids
- Small (< 4 cm) solitary subserosal fibroids

Pelvic Ultrasound: TAU and TVU

A pelvic ultrasound (TAU and TVU) will be performed early in the Screening Period and as early in the menstrual cycle as possible in all subjects, or in the Washout Period, if applicable. Subsequent pelvic ultrasounds will be performed at the time points indicated in Appendix C, Study Activites. 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 ≥ 2 cm (longest diameter), or multiple small fibroids with a uterine volume of ≥ 200 cm^3 to ≤ 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, 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; however, have SIS images which are unable to fully assess the endometrial cavity, may undergo additional imaging modalities such as MRI for further evaluation.

An SIS may be performed during the Treatment Period if there is an intracavitary finding on ultrasound or MRI.

Magnetic Resonance Imaging (MRI) Subset:

A subset of subjects who consent to participate in the MRI Subset will have an MRI performed at the Day 1 (unless an MRI was performed in Screening as indicated below) and Month 6 or Premature Discontinuation visits during the Treatment Period and at the Post-Treatment Follow-Up Month 3 or Post-Treatment Premature Discontinuation Visit.

If the Day 1 MRI cannot be performed within the specified assessment window per Table 1, the MRI should not be performed and the subject will not participate in the MRI Subset. Subjects who have qualifying uterine fibroids and uterine volume as assessed by ultrasound; however, have SIS images which are unable to fully assess the endometrial cavity, may undergo additional imaging modalities such as MRI for further evaluation in Screening.

Subjects who had an MRI prior to Day 1 and agree to be part of the MRI subset, will not have an MRI repeated at Day 1; instead, subjects will have MRIs performed at the Month 6 visit during the Treatment Period and at the Post-Treatment Follow-Up Month 3 Visit.

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

- Fibroid volume in cubic centimeters (of 3 largest fibroids)
- Fibroid location
- Uterine volume in cubic centimeters
- Presence of adenomyosis (diffuse adenomyosis as the dominant condition versus focal)

- Presence of any concerning findings

If the subject prematurely discontinued prior to Month 3, i.e., received < 3 months of study drug during the Treatment Period, an MRI will not be performed at the Premature Discontinuation visit during the Treatment or Post-Treatment Follow-Up Period.

Depending on the size of the uterus, MRI images of the abdominal cavity may need to be submitted to measure uterine volume and to assess for safety. It is recommended to follow standard of care when determining which anatomical sections are to be included in order to prevent incomplete views, thus leading to repeat procedures. Please refer to the Image Acquisition Guidelines for further details.

Intracavitary Uterine Findings

An SIS may be performed during the Treatment or Post-Treatment Follow-Up Periods if the pelvic ultrasound (TAU and TVU) or MRI (if applicable) results suggest an intracavitary lesion such as a polyp. The finding of a polyp during the Treatment or Post-Treatment Periods 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 and Post-Treatment Periods.

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.

During Treatment or Post-Treatment, 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 spine, femoral neck and total hip will be performed by qualified technologist/radiologists utilizing GE Lunar or Hologic equipment and sent to an ICL for review and analysis. Site training and qualifications, including assessment of instruments, will be completed prior to screening the first subject. Instructions on calibration and standardization of instruments will be specified in a manual that will be provided to all study sites. Sites will need to obtain approval from the ICL prior to initiating study scans.

A DXA scan will be performed during the Screening Period to determine eligibility based on BMD measurements from the ICL. Subjects with a T-score of ≤ -1.5 at the lumbar spine, total hip or femoral neck on the screening DXA scan will not be eligible for randomization into the study.

During the Treatment Period, a DXA scan will be performed at Month 6 or Premature Discontinuation visit (Subjects who prematurely discontinue treatment prior to Month 3 will not have a DXA at the Premature Discontinuation Visit unless the premature discontinuation was related to BMD decrease or the occurrence of a fracture). In the event there is a change in DXA machine for a subject between baseline and a subsequent time point, the AbbVie TA MD must be notified.

It is recommended that the bone scan performed for the Month 6 Visit is conducted approximately 15 days prior to the scheduled Month 6 Visit to ensure the results are received from the central vendor in order to determine eligibility for inclusion into the extension study. If DXA results are not available by the Month 6 visit of the Treatment Period, refer to Section 5.4.4 for instructions until results are available to determine eligibility into the extension study.

During the Post-Treatment Follow-Up Period, DXA scans will be performed in all subjects at the Month 6 and Month 12 visits in the Post-Treatment Follow-Up Period. However, if the subject prematurely discontinued prior to the Treatment Month 3 visit, i.e., received < 3 months of study drug during the Treatment Period, Post-Treatment DXA scans will not be performed (unless the premature discontinuation was related to BMD or the occurrence of a fracture) and the subject will complete the study at the Post-Treatment Month 6 visit.

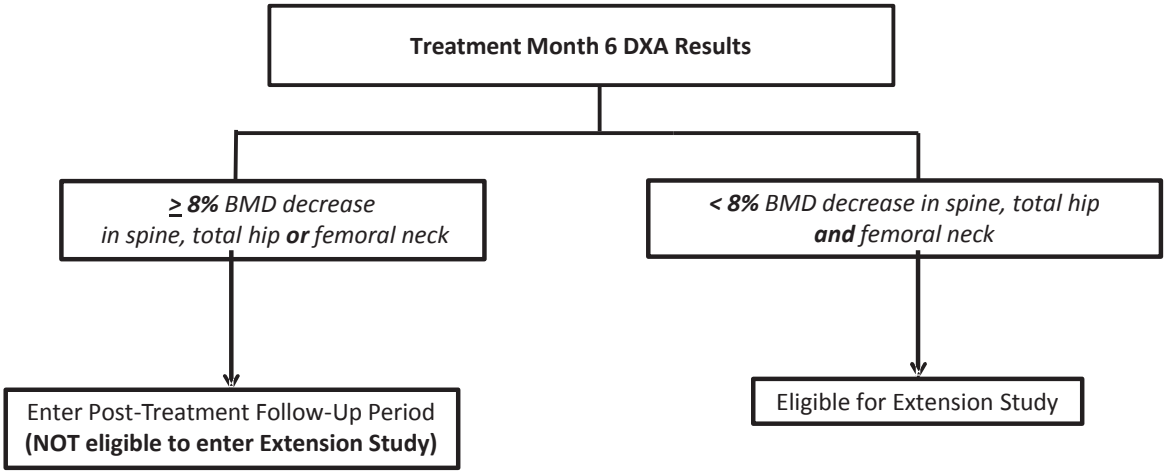
A BMD decrease at any anatomic location (spine, total hip or femoral neck) during the Treatment or Post-Treatment Follow-up period that leads to discontinuation from study or a BMD decrease at any anatomic location with a T-score < –1.5 should be reported as AE.

Determination of BMD Eligibility for Inclusion into the Extension Study:

Inclusion of subjects for BMD criteria in the extension study will be based on the parameters specified below and illustrated in Figure 3.

- Subjects with BMD decrease < 8% in the spine, total hip and femoral neck will be eligible based on DXA for entry into the extension study.
- Subjects with ≥ 8% BMD decrease at any location at Month 6 of the Treatment Period are not eligible for entry into the extension study and will instead enter into the Post-Treatment Follow-Up Period and continue with BMD evaluation as illustrated in Figure 4.

Figure 3. Management of BMD % Decrease at Month 6 of Treatment Period and Eligibility for Inclusion in the Extension Study



Management of BMD for Subjects Entering the Post-Treatment Follow-Up Period

For subjects entering the Post-Treatment Follow-Up Period of this study, DXA scans are required at Month 6 and Month 12 of the Post-Treatment Follow-Up Period.

A Post-Treatment Month 6 or Month 12 DXA will not be performed in subjects who prematurely discontinued prior to the Treatment Month 3 visit, i.e., received < 3 months of study drug during the Treatment Period (unless the premature discontinuation was related to BMD decrease or the occurrence of a fracture).

Management of BMD % Decrease at Post-Treatment Follow-up Month 12

Management of subjects with BMD % decrease at Post-Treatment Follow-Up Month 12 is outlined below and illustrated in Figure 4.

Subjects with Post-Treatment Month 12 BMD % decrease of < 3% in the spine, femoral neck and total hip and no decrease in any region from Post-Treatment Follow-up Month 6 to Month 12 will not require a referral to a bone specialist.

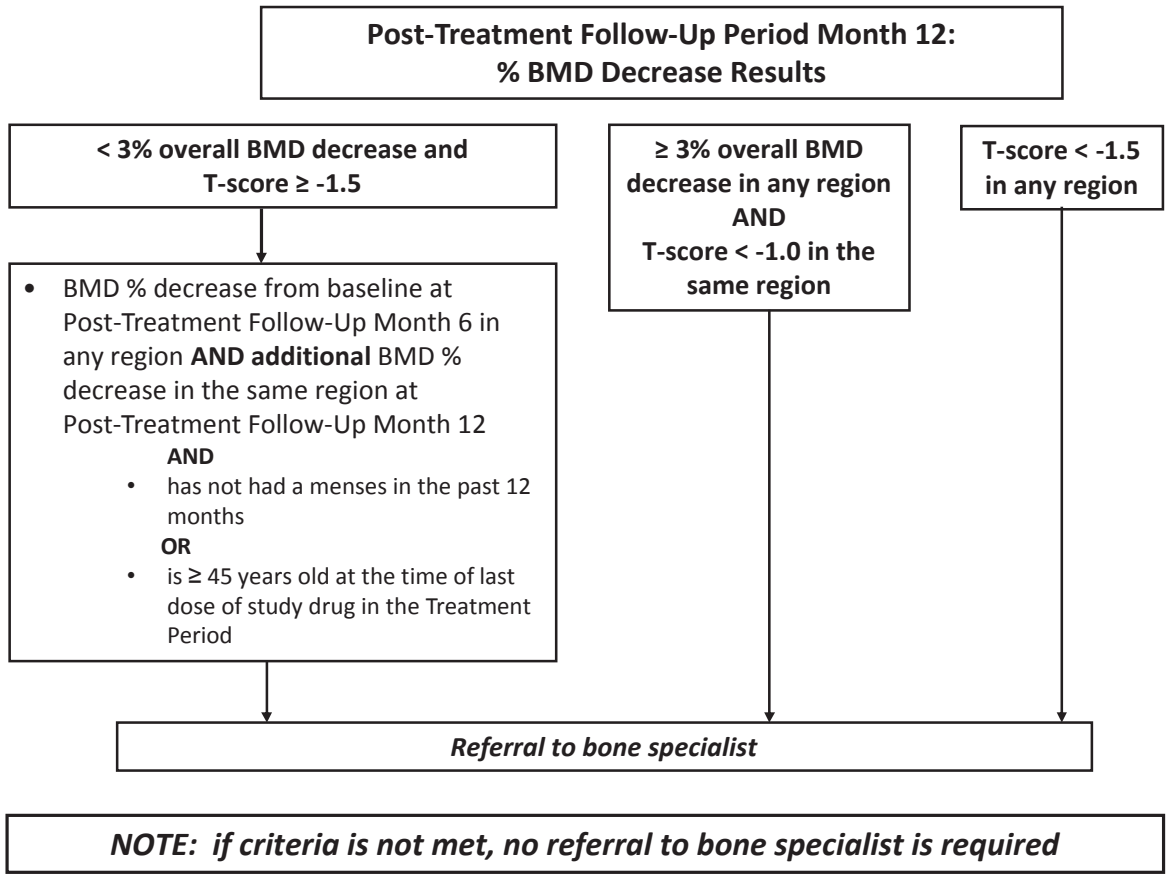
Subjects will be referred to a Bone Specialist at Post-Treatment Follow-up Month 12, even if the overall BMD decrease from baseline is < 3%, if they meet the following criteria:

- Subject had Post-Treatment Month 6 BMD decrease compared to baseline in any region and demonstrates further BMD decrease at Month 12 in the same region (between Post-Treatment Month 6 and Month 12) and, subject meets one of the following:
  - Subject was ≥ 45 years of age at the time of last dose of study drug in the Treatment Period

    OR
  - Subject has not had a menses in the past 12 months
- Subjects with Post-Treatment Month 12 BMD % decrease of ≥ 3% in the spine, femoral neck or total hip and a T-score < –1.0 OR T-score < –1.5 will be referred to a bone specialist for further management, and will be followed on an individual basis.

The management plan for subjects referred to a Bone Specialist (e.g., Endocrinologist, Rheumatologist, International Society for Clinical Densitometry (ISCD) certified physician) will be reviewed with the AbbVie TA MD, with follow-up information provided on the subject evaluation, treatment, and outcome. Follow-up information from the initial evaluation will be recorded in the eCRF. It is recommended that the Bone Specialist should be someone other than the Principal Investigator or Sub-Investigator.

Figure 4. Management of BMD % Decrease: Post-Treatment Follow-Up Month 12



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 Inorganic phosphorus Magnesium Total protein Albumin Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALAT) Serum glutamic-oxaloacetic transaminase (SGOT/ASAT) Alkaline phosphatase Uric acid Lactate dehydrogenase Creatine Phosphokinase Serum iron Serum ferritin Total iron binding capacity (TIBC)	Specific gravity Ketones Protein Blood Glucose pH Microscopic Exam
		Urine%
		Gonorrhea Chlamydia
		Lipid Panel (After Minimum 8-Hour Fast)
		LDL cholesterol HDL cholesterol Triglycerides Total cholesterol
		Lipid Profile
		Apolipoprotein A and B
Pregnancy Test		
Serum pregnancy		
Endocrine Panel	**Serology Testing**	**PK and PD Assay/PG Analysis**
Follicle-stimulating hormone (FSH) Luteinizing Hormone (LH) Reflexive Thyroid Stimulating Hormone (TSH) Thyroxine Binding Globulin (TBG)	HAV-IgM HbsAg HCV Ab HIV Ab	Elagolix and NETA* E2 and P* DNA and RNA*

* Samples will be shipped to the Central Laboratory by the Study Site and then shipped by the Central Laboratory to AbbVie for analysis.

% Optional – ordered at Investigator's discretion. Samples will be shipped to the Central Laboratory.

All laboratory samples (hematology, chemistry, urinalysis, endocrine panel, lipid panel) will be assessed using a certified central laboratory 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 recordings are conducted at a visit. 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 lab. Residual serum samples remaining after chemistry testing has been performed will be stored frozen at the central laboratory for possible repeat testing or further analysis upon AbbVie's request.

The laboratory results (except Apo A and Apo B) 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 indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). The Investigator will assess 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 6.1).

All screening laboratory results must be reviewed prior to randomization, including any repeated test results. Subjects will not be randomized if laboratory results are clinically significant. 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 events.

Blood samples for Pharmacogenetic (PG), Pharmacokinetic (PK), and Pharmacodynamic (PD) analysis will be collected and processed as indicated in Section 5.3.1.2 (PG), Section 5.3.1.3 (PD) and Section 5.3.2 (PK).

Safety Laboratory Tests

Clinical safety laboratory tests consist of hematology, clinical chemistry, including lipid panel and urinalysis samples. The clinical chemistry and lipid panel samples should be obtained in the morning following an overnight fast (minimum of 8 hours); however,

there may be circumstances when a sample is obtained later in the day and/or not under fasting conditions. If a sample was obtained 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.

Lipid Panel

If, during the Treatment or through Post-Treatment Period Month 12 Visit the lipid panel results for LDL cholesterol, Triglycerides, Total cholesterol are more than 3 × the upper limit of normal range and the sample was not obtained under fasting conditions (minimum 8 hour fast), the subject will return to the office as soon as possible to have the panel repeated under fasting conditions.

Apolipoprotein A and B, (Apo A and Apo B)

Blood samples for Apo A and Apo B will be collected as part of the chemistry panel. The Apo A and Apo B data are exploratory and results will not be provided to the investigative site.

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 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.

HIV testing will be conducted by ELISA; if the test result is reactive, testing will automatically reflex to Multispot assay. If results are negative or indeterminate, HIV-1 TMA assay is performed to complete the confirmation with results of: Not Detected or Detected. If the HIV ELISA test result is reactive or TMA assay results are detected, the subject will be screen-failed.

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

Urine Test for Gonorrhea and Chlamydia (Optional)

Gonorrhea and chlamydia testing can be ordered at the Investigator's discretion during the Screening Period, to test for active gonorrhea or chlamydia prior to undergoing the endometrial biopsy and SIS. Any treatment provided will occur outside of the protocol.

Endocrine Panel

The endocrine panel consists of the following analytes: FSH, LH, reflexive TSH and thyroxine-binding globulin (TBG).

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. Subjects will continue to collect sanitary products after eligibility based on MBL in Screening is determined. There will be no interruption in collection of sanitary products between Screening and Randomization and the Subject should be instructed to collect sanitary products starting in Screening and throughout the 6-month Treatment Period to determine the change from baseline in MBL volume, and up through their first menses with full menstrual flow in the Post-Treatment Follow-up Period to assess return to menses.

Starting in Screening, subjects will be dispensed sanitary collection kits that consist of validated sanitary products, product collection bags, bar-coded labels and a keg with screw-on lid for storage as provided by the vendor. It is important that only the sanitary

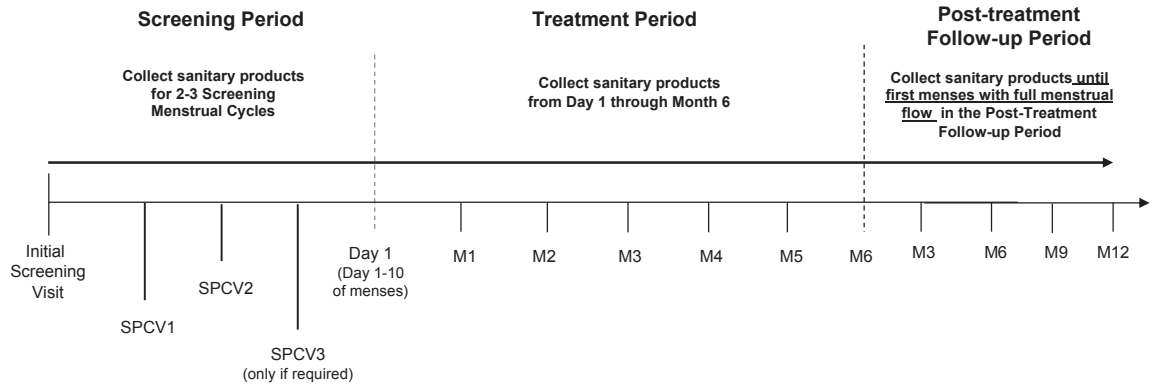
products provided for use during the study are used. Validated sanitary products may include:

- 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, Treatment and Post-Treatment Periods are outlined in Figure 5.

Figure 5. Sanitary Product Dispensation and Collection



- SPCV= Screening Cycle Product Collection Visits (1, 2 and 3)
- All products should be returned to the study site within approximately 5 days after all bleeding and/or spotting has ended
- SCPCV3 may not be required depending on amount of blood loss during SPCV 1 and SPCV2
- Subjects will continue collecting sanitary products from Screening through the first menses with full menstrual flow in the Post-Treatment Follow-up Period. There will be no break in collection between Screening and Randomization.

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, 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.

Under very limited conditions, 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 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

* Study site must consult AbbVie for approval to collect sanitary products for additional menstrual cycles in screening.

\# 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.

Sites will contact the Interactive Response Technology (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 the initial shipment of study drug to the study site.

Sanitary Product Collection During the Treatment Period

During the Treatment Period, Subjects will continue to collect sanitary products on all days with menstrual bleeding or spotting.

As in Screening, sanitary products collected during the Treatment Period will be returned by the Subject within approximately 5 days after cessation of menstrual bleeding or spotting and a venous sample will be obtained at either a scheduled monthly visit or at a Product Collection Visit, as appropriate.

Treatment Period Product Collection Visits

Product Collection Visits are only necessary if a monthly visit is not scheduled to occur within approximately 5 days after cessation of menstrual bleeding or spotting. During the Product Collection Visits, subjects will have a venous blood sample, urine pregnancy test, vital signs, contraception counseling, as well as adverse event and concomitant medication assessment. Product Collection Visits during the Treatment Period should be

numbered in sequential order (e.g., Product Collection Visit 1, Product Collection Visit 2, etc.) and entered into the eCRF.

Subjects who do not return a sanitary product collection keg at a site visit (scheduled monthly visit, PCV or Unscheduled Visit) will be administered the UBQ by the Site Staff. The Site Staff will ask the subject if she had any bleeding or spotting since the previous visit. If the subject did have bleeding or spotting since the previous visit, the site staff will ask why the subject did not return sanitary products. Responses to these questions will be documented on the UBQ by the Site Staff.

Sanitary Product Collection During the Post-Treatment Follow-Up Period

Subjects will be required to collect sanitary products on days with menstrual bleeding or spotting for their first menses with full menstrual flow in the Post-Treatment Follow-up Period. If the subject misses collecting sanitary products for her first full menses, she will be required to collect sanitary products for her next full menses. Once a subject has submitted sanitary products from her first full menses in the Post-Treatment Follow-up Period, she will no longer be required to collect sanitary products during her subsequent menses.

Subjects who have not returned to their first full menses and have not returned a sanitary product collection keg in the Post-Treatment Follow-up Period will be administered the UBQ by the Site Staff. The Site Staff will ask the subject if she had any bleeding or spotting since the previous visit. If the subject did have bleeding or spotting since the previous visit, the site staff will ask why the subject has not returned for a Post-Treatment Product Collection Visit to return her sanitary products. Responses to these questions will be documented on the UBQ by the Site Staff. Once a Subject returns sanitary products from a full menses in the Post-Treatment Follow-up Period, the Post-Treatment UBQ no longer needs to be completed.

Return of Sanitary Products to Alkaline Hematin Vendor

The site will submit the sanitary products and venous blood sample collected at the scheduled monthly visits or Product Collection Visits to the Alkaline Hematin Lab for analysis as outlined in the Alkaline Hematin Laboratory Manual.

Home Visits

There may be an option for subjects to have a Product Collection Visit conducted at home by a Home Health Care Agent who will go to the Subject's home to draw a venous blood sample and retrieve the collection keg to return to the site.

Use of Non-Validated Products

All subjects are to only use validated products, however in cases when a subject used non-validated (a product not provided for use in the study), the subject should be instructed to collect and submit the non-validated products to the Study Site.

Subjects Pending Results for Eligibility into the Extension Study

Site Staff should continue to dispense sanitary products and sanitary product collection kits to subjects if results for entry into the extension study are pending at the time of the Month 6 visit.

Sanitary products collected after the Month 6 visit will be returned to the site within approximately 5 days after cessation of menstrual bleeding or spotting as a Product Collection Visit and this collection will be numbered sequentially (refer to the Treatment Period Product Collection Visit section above).

Refer to Figure 5, Sanitary Product Dispensation and Collection for details on dispensation and collection requirements.

Patient Reported Outcomes (PRO) Rating Scales

Prior to the start of the study, Site Personnel will be trained on all rating scales used in this study. 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. Subjects and Site Staff will be asked to record their responses directly onto paper questionnaires and enter into the eCRF.

Reason for Study Participation

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

Physician Surgery Questionnaire

Each physician will be asked to complete the Physician Surgery Questionnaire (PSQ) (Appendix F) at the Day 1 Visit.

The PSQ evaluates 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 Bleeding Questionnaire (Treatment – UBQ)

Subjects who did not return a Sanitary Product Collection Keg (for alkaline hematin analysis) at a site visit (scheduled monthly visit, PCV or Unscheduled Visit) during the Treatment Period, will be asked to indicate whether they had any uterine bleeding or spotting since their last study visit. If the subject did not have uterine bleeding or spotting the site staff will indicate "No" on the UBQ. If the subject did have bleeding or spotting, the subject will be asked the reason they did not return sanitary product collection keg. This response will be recorded on the UBQ (Appendix G) by the Site Staff.

Post-Treatment Uterine Bleeding Questionnaire (Post-Treatment-UBQ)

Subjects who have not collected and returned sanitary products for their first menses with full menstrual flow in the Post-Treatment Follow-up Period, will be asked at each visit before sanitary products are returned if they had any bleeding or spotting since their last visit. If the subject did not have uterine bleeding or spotting the site staff will indicate "No" on the UBQ. If the subject did have bleeding or spotting, the subject will be asked the reason she did not return the sanitary product collection keg. This response will be recorded on the UBQ (Appendix H) by the Site Staff. Once a Subject returns sanitary products from a full menses in the Post-Treatment Follow-up Period, the Post-Treatment UBQ no longer needs to be completed.

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

The UFS-QoL (Appendix I) 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 modified (4-week recall) UFS-QoL Questionnaire[10] 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 (Appendix J) 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.

Patient Global Impression of Change – Non-Bleeding Uterine Fibroids Symptoms (PGIC-NBUFS)

Subjects will complete the PGIC-NBUFS (Appendix K) to document the presence of and to assess the change in the overall severity of non-bleeding uterine fibroid symptoms and the severity of specific non-bleeding uterine fibroid symptoms (from very much improved to very much worse) since initiation of study drug.

Work Productivity and Activity Impairment Questionnaire (WPAI)

The WPAI questionnaire (Appendix L) will consist of questions measuring the impact of uterine fibroid symptoms on work productivity and daily activities during the previous 7 days. The questionnaire will be completed by Study Subjects at the Day 1 and Month 6 visits.

EuroQol-5D 5 level (EQ-5D-5L™)[11]

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

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The Screening-Baseline C-SSRS (Appendix N) questionnaire will be administered in Screening and Day 1. During the Treatment Period, the C-SSRS, Since Last Visit (Appendix O) questionnaire will be administered as 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 at the times outlined in Appendix C. The C-SSRS administered at the Day 1 Visit will serve as the baseline for clinical assessment.

Health Care Resource Utilization (HCRU)

The Health Care Resource Utilization questionnaire (Appendix P) will be used to capture routine/general health care visits (that are not associated with an adverse event) to non-study Health Care Providers during the Treatment Period. Subjects will be asked to provide information on any visits to non-study Health Care Practitioners in the past 4 weeks for routine/general health visits including any diagnostic or therapeutic procedures that were performed. The responses will be recorded on the HCRU by the Site Staff. Health care resource use related to an Adverse Event or Serious Adverse Event will be captured as part of the Adverse Event, independent of the HCRU, and recorded in the eCRF.

Complete HCRU Version 1.0 (Appendix Q) for subjects randomized on Day 1 under Protocol Amendment 1 at the timepoints listed in Appendix C, Study Activities.

Complete HCRU Version 2.0 (Appendix P) for subjects randomized on Day 1 under Protocol Amendment 2 at the timepoints listed in Appendix C, Study Activities.

Phone Contact During the Post-Treament Follow-Up Period

During the Post-Treatment Follow-Up Period at Follow-Up Months 2, 4, 5, 7, 8, 10, and 11, site staff will telephone subjects who have not discontinued from the Follow-Up Period. Site staff will assess ongoing adverse events, concomitant medications, provide contraception counseling and obtain the result of the subject-administered urine pregnancy test. Site staff will also assess return to full menses and administration of the Post-Treatment UBQ, as applicable. The phone call and pregnancy test result will be documented in source documents and eCRF.

Randomization and Assignment of Subject Numbers

The site will contact IRT during the Washout or Screening Period to obtain a subject (Screening) number after the subject has signed the informed consent. Consecutive and unique subject numbers 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 3 treatment groups by using IRT and providing the subject number the subject received during Screening or Washout. During the randomization contact, a randomization number and kit number 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 monthly visit in IRT in order to obtain a 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. 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 or the Extension Study M12-816.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

One 4 mL whole blood sample for DNA isolation will be collected on Day 1 from each subject with consent. If the sample is not collected on Day 1, it may be collected at any time throughout the study.

Additionally, one 2.5 mL whole blood sample for RNA isolation will be collected on Day 1, Month 1, Month 3, and Month 6 or premature discontinuation with consent. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

The samples will be minimally labeled with study ID, subject ID, and time-point. Please refer to the Lab manual for instructions on collection and processing of samples.

Samples will be shipped frozen to the central laboratory and later shipped to AbbVie for DNA/RNA extraction.

AbbVie will store the DNA and RNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on ABT-620 (or drugs of this class) continues, but no longer than 20 years.

5.3.1.3 Collection and Handling of Pharmacodynamic Variables

Blood Samples for Estradiol (E2) and Progesterone (P) Assay

A single blood sample will be collected at each timepoint indicated in Appendix C to be used for the pharmacodynamic analysis of E2 and P. The blood samples for assay of estradiol and progesterone will be collected in one 9 mL evacuated collection tube without anticoagulant (red cap, no gel separators to be used). Sufficient blood volume will be collected to provide approximately 4 mL serum from each sample.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing and shipment.

On Day 1, estradiol and progesterone 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.

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 3 mL evacuated K_2-ethylenediaminetetraacetic acid (K_2EDTA)-containing collection tubes at the time points indicated in Appendix C. Sufficient blood will be collected to provide approximately 1 mL plasma from each sample.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing and shipment.

The date and time of collection will be recorded on the Central Laboratory Requisition Form. The Day 1 visit sample should be collected approximately 1 hour after the first dose of study drug is administered; samples collected on other visit days will be collected at any time during the visit.

5.3.2.2 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Primary Efficacy Variable

The primary endpoint will be the percentage of subjects meeting a composite endpoint consisting of these two bleeding assessments:

- MBL volume of < 80 mL during the Final Month (the last 28 days of treatment), AND

- 50% or greater reduction in MBL volume from baseline to the Final Month (the last 28 days of treatment)

A subject who prematurely discontinues the study drug due to adverse events, "lack of efficacy" or "requires surgery or invasive intervention for treatment of uterine fibroids" will be considered as a non-responder regardless whether she meets the two aforementioned responder criteria or not.

5.3.3.2 Secondary Efficacy Variable

The following will be considered secondary variables:

- MBL volume assessed using AH methodology and UBQ
- Suppression of bleeding
- Hemoglobin concentration
- Fibroid and uterine volume

5.3.4 PRO and Quality of Life Variables

- UFS-QoL Questionnaire
- Physician Surgery Questionnaire
- EuroQol (EQ-5D-5L) Questionnaire
- Health Care Resource Utilization (HCRU)
- Patient Global Impression of Change (PGIC) Questionnaires
- Work Productivity and Activity Impairment (WPAI) Questionnaire
- Reason for Study Participation Questionnaire

5.3.5 Safety Variables

- Change from baseline to Month 6 in bone mineral density 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) (e.g., hypoestrogenic adverse events)
- Time to the first post-treatment menses
- 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)

5.3.6 Pharmacodynamic Variables

Concentrations of E2, P, LH and FSH will be obtained throughout the Screening and Treatment Periods. Additional pharmacodynamic parameters may be calculated if useful in the interpretation of the data.

5.3.7 Pharmacokinetic Variables

Exposures of elagolix and norethindrone, may be determined using a population PK approach. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.8 Pharmacogenetic Variables

DNA and RNA samples may be sequenced and data analyzed for RNA expression and genetic factors contributing to the subject's response to elagolix, or other study treatment, in terms of pharmacokinetics, efficacy, tolerability and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, or other genes believed to be related to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to elagolix or drugs of this class. The samples may also be used for the development of diagnostic tests related to elagolix (or drugs of this class). The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.9 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be employed for this Phase 3 study and will have the usual responsibilities for safeguarding the interests of study participants and monitoring the overall study conduct. The IDMC will provide recommendations about continuing, modifying, or stopping the trial for safety reasons. The IDMC membership and responsibilities will be documented in its charter. After each IDMC meeting, the IDMC will communicate its recommendations to the sponsor, as described in the IDMC charter.

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 period these procedures do not warrant withdrawal if performed during the Post-Treatment Period unless a hysterectomy with bilateral salpingo-oophorectomy (BSO) is performed and the Subject does not plan to use Hormone Replacement Therapy within 1 month of the surgery date.
- The subject becomes pregnant.

- The subject has (SGPT/ALAT) or SGOT/ASAT elevation > 5 times the upper limit of normal confirmed upon repeat during the Treatment Period.
- The subject's legally acceptable representative decides to withdraw consent for any reason.
- Heavy menstrual bleeding during the Treatment Period that requires a blood transfusion at any time after having taken 28 days of study drug. If a subject has a blood transfusion during the Post-Treatment Period, the AbbVie TA MD should be contacted to determine if the subject can remain in the study.
- Any other medical reason that AbbVie or the study 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 Treatment Period 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 12-Month Post-Treatment Follow-Up Period.

In the event that a subject withdraws or is prematurely discontinued during the Post-Treatment Follow-Up period, the subject should complete the Post-Treatment Premature Discontinuation Visit as soon as possible and undergo study procedures as outlined in Appendix C. These procedures should not interfere with the initiation of any new treatments or therapeutic modalities the Investigator determines are necessary to treat the subject's condition. The reason(s) for the discontinuation from the study will be recorded in the eCRFs.

All used and unused study drug containers will be returned to the study site.

If a subject becomes pregnant during the Treatment or Post-Treatment Follow-Up Periods, 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 from treatment and enter Post-Treatment Follow-Up and received study drug for < 3 months or the procedure was performed in the past two months are not required to undergo the following procedures during the Post-Treatment Period, unless requested by the AbbVie TA MD or based on clinical judgment:

Post-Treatment Period Month 3:

- TAU/TVU
- MRI

Post-Treatment Period Month 6:

- TAU/TVU
- DXA (unless the premature discontinuation was related to BMD decrease or the occurrence of a fracture)

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.

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

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 7 or more consecutive days of dosing (with either ABT-620/Placebo or E2/NETA/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.

5.4.4 Delays in Rollover into the Extension Study

Subjects may be required to remain in the Treatment Period following the completion of the Month 6 visit if results to determine eligibility into the Extension Study are not available at the time of the Month 6 visit. Subjects will return to the study site at the same 28-day monthly visit intervals if eligibility for the extension study has not been determined before then. Subjects will continue to take study drug until eligibility has been established. These visits will be documented as and registered as Unscheduled Visits. Sites should register Unscheduled Visits in IRT in order to obtain additional kits of study drug. Procedures/assessments to be performed during the Unscheduled Visit while the subject is waiting for the determination of eligibility into the extension study, are indicated in the Table 6.

Table 6. Schedule of Assessments – Delays in Roll-Over into Extension Study

Schedule of Assessments – Delays in Roll-Over into Extension Study		
Procedure		**Perform Monthly**
Symptom-directed Physical Examination		X
Vital Signs		X
Clinical/Safety Laboratory Tests: Hematology, Chemistry[a]		X
Urine Pregnancy Test[b]		X
Endocrine Panel: FSH, LH		X
Pharmacodynamic Sample (PD): Serum Estradiol (E2) and Progesterone (P)		X
Contraception Counseling and Dispense Contraceptives as necessary		X
Dispense Sanitary Products and Collection Kits (Keg, Collection Bags etc.)		X
Collect and Return Sanitary Products		X
Register Visits in IRT		X
Study Drug: Dispense (D) and Return (R)[c]		X
Study Drug Accountability		X
Study Drug Compliance		X
Adverse Event Monitoring		X
Concomitant Medication Monitoring		X
Questionnaires	UBQ[d]	X
	C-SSRS – Since Last Visit	X
	HCRU	X

a. Eight (8) hour minimum fast for Clinical Safety Laboratory Tests; Chemistry and Lipid Panels.

b. 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 subject will be discontinued from the study at the point the pregnancy was confirmed.

c. Urine pregnancy test must be negative prior to providing subjects with their next monthly supply of study drug.

d. The Uterine Bleeding Questionnaire (UBQ) is to be completed by Site Staff at every scheduled monthly visit (or PCV) only if the subject did not return a sanitary product collection keg at the visit.

Once eligibility for entry into the extension study has been determined:

Subject Entering the Extension Study:

- Subject will return to the study site as soon as possible

- Subject will discontinue taking study drug from the pivotal study just prior to entering the extension study, i.e., subjects are to continue taking study drug until they have returned to the site for their roll-over visit
- Record transition of study subject into the extension study in IRT

Subject NOT Entering the Extension Study:

- Subject will discontinue taking study drug
- Subject will return to the study site as soon as possible
- Record transition of study subject into the Post-Treatment Follow-up Period in IRT
- The next scheduled visit will be the Month 1 Site Visit

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 6 months of treatment:

- placebo (n = 100)
- elagolix 300 mg BID (n = 100)
- elagolix 300 mg BID plus E2/NETA (estradiol 1.0 mg/norethindrone acetate 0.5 mg) QD (n = 200)

The treatment administration is presented in Table 7.

Table 7. Treatments Administered

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

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). Subjects will be instructed to self-administer their study drug throughout the 6-month Treatment Period.

A 1-month supply of each study drug (plus 1 week extra) will be dispensed during the Treatment Period at the Day 1 (randomization) Visit, and at the Month 1, 2, 3, 4 and 5 visits.

Study drug will be taken orally twice daily for the entire 6-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 in order to promote compliance.

If the subject forgets to take the morning dose, she should be instructed to take the morning dose as soon as possible and take the evening dose as scheduled. If the subject

forgets to take the evening dose, she should be instructed to take the evening dose as soon as possible; if the subject misses the evening dose completely (until the next morning), the subject should only take the 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 monthly visit.

At the Month 6 visit, a –4 or +6 day visit window will be allowed in order to collect sanitary products from the last menstrual bleeding cycle prior to the Month 6 visit if menstrual bleeding starts immediately prior to or coincides with the scheduled visit. If the +6 day window is needed, the subject will be instructed to continue taking study drug from the extra blister card (1 week supply) until she returns for the Month 6 Visit.

Subjects awaiting results to determine eligibility into the extension study will continue to be dispensed study drug until results are available. Refer to Section 5.4.4 for further details on dispensing and registering subjects during this waiting period.

5.5.2 Identity of Investigational Products

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

Table 8. Identity of Investigational Products

Study Drug	Formulation	Route of Administration	Trademark	Manufacturer
Elagolix	Film-coated 300 mg tablets	Oral	N/A	AbbVie
Matching Elagolix Placebo	Film-coated Placebo tablets	Oral	N/A	AbbVie
E2/NETA*	Estradiol 1.0 mg/Norethindrone acetate 0.5 mg capsules*	Oral	N/A	Commercial Tablets: Pharmaceutics International, Inc
Matching E2/NETA Placebo	Placebo capsules	Oral	N/A	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). Two kits of study drug will be provided at each dispensing visit. One kit consists of Elagolix or matching placebo and the other kit consists of E2/NETA capsules or matching placebo. 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.

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

5.5.2.2 Storage and Disposition of Study Drug

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

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 for a total of 6 months of treatment.

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 into one of the three 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 or unused) at the subsequent visit.

5.5.5 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 personnel and subject will remain blinded to each subject's treatment throughout the course of the study. The IRT will provide access to blinded subject treatment information during the study.

AbbVie must be notified before the blind is broken, unless identification of the study drug is required for medical emergency; i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours 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

Subjects will be instructed to return all study drug kits (used or unused) to the study site personnel at the Month 1, Month 2, Month 3, Month 4, Month 5 and Month 6 or Premature Discontinuation Visits during the Treatment Period. The study site personnel will document compliance.

The investigator or his/her designated and qualified representatives will 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 those described in the protocol.

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. Daily recordings of study drug dosing will be obtained using a compliance packaging blister card for all subjects (for both elagolix/matching placebo and E2/NETA/matching placebo). AbbVie will provide training and study drug compliance materials to sites for instructing subjects on study drug compliance.

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

Sites should instruct subjects not to remove extra or multiple medications from the blister cards all at once and should only remove the study drug from the blister when it is the time to take the dose. If the compliance data shows incidence of removing a number of extra 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.

During review of the study drug compliance with the study subject, if 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 should be provided by the subject and recorded in the source documents.

If a subject missed more than 7 consecutive days of taking study drug, the AbbVie TA MD should be notified to determine whether the subject may continue.

Compliance packaging data will be used for exposure response analysis.

5.5.7 Drug Accountability

The study Investigator or designee will verify by signature and date that study drug supplies are received intact and in the correct amounts indicated on the shipping document Proof of Receipt or similar shipping document or via direct recording in IRT. 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 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, Proof of Receipt 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 and unused containers will be returned to AbbVie according to instructions from AbbVie.

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

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This Phase 3 study will be conducted as a randomized, double-blind, multi-center, placebo-controlled study in premenopausal women 18 to 51 years of age with HMB associated with uterine fibroids. The randomized, double-blind, placebo-controlled study design is the standard for unbiased assessments of treatment group differences.

This study will evaluate the safety and efficacy of elagolix 300 mg BID alone and elagolix 300 mg BID in combination with E2/NETA QD (1.0 mg/0.5 mg) versus placebo in subjects with HMB associated with uterine fibroids. The study will also assess the impact of E2/NETA on the efficacy, safety, and tolerability of elagolix, including hypoestrogenic side effects such as BMD decrease and vasomotor symptoms.

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 51 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 51 is included to reduce the risk of subjects becoming menopausal during the study. No studies in males or in females outside of the reproductive years are necessary for this proposed indication.

5.6.4 Selection of Doses in the Study

The preliminary results of the 3-month Phase 2a dose finding, 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 to date.

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 6.1.5. 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 personnel, or reported spontaneously by the subject will be recorded.

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 vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention and/or if the investigator considers them to be adverse events.

An adverse event of amenorrhea will be reported for subjects who do not return to menses by the Post-Treatment Follow-up Month 2 Phone Visit and the adverse event will be followed until resolution. The onset date of the adverse event will be the date of the Follow-up Month 2 Visit.

A BMD decrease at any anatomic location (spine, total hip or femoral neck) during the Treatment or Post-Treatment Follow-up period that leads to discontinuation from study or a BMD decrease at any anatomic location with a T-score < –1.5 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

Some adverse events, such as adverse events of special interest (AESI), such as rash/hypersensitivity, fracture, neuro-psychiatric (depression, mood swings, etc.), vasomotor symptoms (hot flush, night sweats) or serious adverse events. 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	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

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.

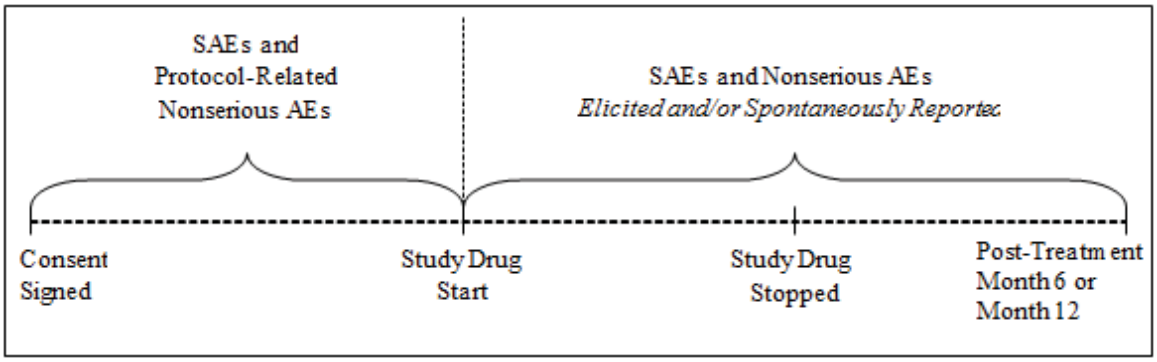
6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration through Month 6 or Month 12 in the Post-Treatment Follow-Up Period, (if applicable) will be collected, whether solicited or spontaneously reported by the subject. 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.

If a subject prematurely discontinues from the study, i.e., either prematurely discontinues from Treatment Period and does not enter the Post-Treatment Follow-Up Period or prematurely discontinues from the Post-Treatment Follow-Up Period, adverse events and serious adverse events will be collected up to 30 days after the last dose of study drug.

Adverse event information will be collected as shown in Figure 6.

Figure 6. Adverse Event Collection



6.1.5 Adverse Event Reporting

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

Email:	[redacted]
FAX to:	

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 emailing (preferred route) or faxing the appropriate serious adverse event forms to:

Email: [redacted]
FAX to:

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

Men's and Women's Health Safety Team

AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Men's and Women's Health Safety Line
[redacted]

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

Primary Therapeutic Area Medical Director (TA MD):

[redacted]

In emergency situations involving study subjects when the primary AbbVie 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 medical monitor:

Phone:	[redacted]
Email:	

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. If a serum pregnancy test result is positive at any time during the Treatment Period of the study, the site will immediately inform the subject to discontinue study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for any study subject with a positive serum pregnancy test from the signing of the informed consent (i.e., washout [if applicable]) or screening) through the Post-Treatment Follow-Up Period. 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 and at the first post-delivery pediatrician visit.

If the subject becomes pregnant during the Treatment or Post-Treatment Follow-Up Periods of the study, an ultrasound examination will be performed as early as possible during the first trimester of pregnancy to assess the conception date and document an intrauterine pregnancy. The following information on the outcome of the pregnancy that occurred after signing of the informed consent, regardless of when the subject became pregnant (i.e., either during the Washout, Screening, Treatment or Post-Treatment Follow-Up Periods) should be collected: fetal outcome (e.g., spontaneous or elective abortion, live infant or still birth), date of delivery, birth weight, birth length, gender, birth

defects, 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 6 to 12 months after delivery.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of 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 (e.g., 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 recorded in source documents as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (investigational product). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

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

7.0 Protocol Deviations

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

Primary Contact: Alternate Contact:

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 General Considerations

The SAS system will be used to perform the statistical analyses. All statistical tests will be two-sided and a significance level of 0.05 will be used unless otherwise specified. A test will be deemed statistically significant if the *P* value rounded to three decimal places is less than or equal to 0.05 unless otherwise specified. The primary safety and efficacy comparisons will be between the elagolix 300 mg BID plus E2/NETA treatment group and the placebo group. Comparisons between the elagolix 300 mg BID alone treatment group and the placebo group are provided for a reference.

8.1.2 Data Sets Analyzed

Modified Intent-to-Treat (mITT) Analysis Set

The modified intent-to-treat (mITT) analysis set is comprised of all randomized subjects who took at least one dose of the study drug and have at least one post-baseline visit in this study. The mITT analysis set will be used for all efficacy analyses unless otherwise specified in the Statistical Analysis Plan (SAP).

Safety Analysis Set

The safety analysis set includes all randomized subjects who took at least one dose of the study drug. The data from the safety analysis set will be presented by the treatment actually received no matter what treatment group was assigned at the time of randomization. If a subject takes more than one treatment, the subject will be analyzed in the safety analysis set as taking the treatment to which she is randomized to. All safety analyses will be performed based on the safety analysis set unless otherwise specified in the SAP.

8.1.3 End-of-Treatment Period Analysis

An end-of-treatment period analysis of the primary and secondary efficacy variables along with demographic and safety variables will be performed after the last subject randomized in this study completes the 6-Month Treatment Period of Study M12-815. This end-of-treatment period analysis will include all treatment period data from all patients randomized into the study. The data base will be versioned and any discrepant data will be clarified before the lock. Analyses will be performed by an external Independent Data Analysis Center (IDAC). Subjects completing Study M12-815 are eligible to be enrolled in the double-blind extension study. The blinding at the subject level for the extension study will be maintained as the efficacy data analyses will only present overall treatment group results to the sponsor. The sponsor will have access to the unblinded results at the treatment group level. However, the blinded data at the subject level will not be included in the results of the demographic, efficacy, or safety endpoints provided to the sponsor. The randomization schedule for Study M12-815 will be provided to the IDAC by someone other than the project statistician, who is otherwise not involved with this study. All AbbVie study personnel will remain blinded until the blind is broken for the double-blind extension study. The end-of-treatment period analysis will only include data collected during the 6-month treatment period of the study and will not include data collected during the post-treatment follow-up period.

Since this end-of-treatment period analysis is the only and final analysis of the primary and ranked secondary endpoints of Study M12-815, no adjustment of alpha-level is necessary.

8.1.4 Independent Data Monitoring Committee

The IDMC will receive an analysis summary by treatment group, which will include data on enrollment, baseline characteristics, and safety.

8.1.5 Demographic, Baseline Characteristics and Concomitant Medications

Demographic and baseline characteristics will be summarized by treatment group.

Overall comparability among treatment groups will be performed using the following methods: a one-way analysis of variance (ANOVA) with treatment group as the main effect for continuous variables, Fisher's exact test (or its generalization to r × c tables) for qualitative categorical variables and the Cochran-Mantel-Haenszel (CMH) row mean scores test for ordered categorical variables.

Medical history will be summarized by condition/diagnosis by treatment group (no treatment group comparisons will be made). 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.

The baseline MBL volume will be defined as the mean of MBL volume from the qualified menstrual cycles during the Screening Period prior to the first study drug dose date, in which the total MBL volume is from all validated and non-validated sanitary products that subjects returned and where the total MBL volume of validated sanitary products only (excluding non-validated sanitary products) is greater than 80 mL. All menstrual cycles during the Screening Period in which the total MBL volume of validated sanitary products only is less than or equal to 80 mL are not qualified to be considered for baseline. The baseline for bleeding days will be based on the assessments from the qualified menstrual cycles that are used to calculate the baseline MBL volume.

The baseline values for other variables will be defined as the last non-missing assessment obtained prior to the initiation of the study drug unless otherwise specified.

8.1.6 Time Points, Time Windows and Time Periods for Analysis

As appropriate, time windows for various safety and efficacy analyses will be defined in the SAP.

For randomized subjects who received at least one dose of the study drug, Study Day is defined as the number of days since (positive values) or prior (negative values) to the first study drug dose. The day of the first study drug dose is defined as Study Day 1, while the last day prior to the first study drug dose is defined as Study Day –1. There is no Study Day 0.

8.1.7 Efficacy

8.1.7.1 Primary Efficacy Variable

8.1.7.1.1 Primary Analysis

The primary analysis of the primary endpoint will be performed using the mITT analysis set.

The primary endpoint will be the percentage of subjects meeting a composite endpoint consisting of two bleeding assessments:

- Menstrual blood loss (MBL) volume < 80 mL during the Final Month (the last 28 days of treatment), and
- 50% or greater reduction in MBL volume from baseline to the Final Month (the last 28 days of treatment).

A subject who prematurely discontinues the study drug due to adverse events, "lack of efficacy," or "requires surgery or invasive intervention for treatment of uterine fibroids" will be considered as a non-responder regardless whether she meets the two aforementioned responder criteria or not.

Baseline MBL volume is described in Section 8.1.5. The Final Month is defined as the last 28 days of treatment prior to and including the last dose date.

The MBL volume used for the primary and sensitivity analyses is defined as the total combined volume of blood ascertained via the AH method from all used (validated and non-validated) sanitary products that a subject returns. In case a subject does not return any used sanitary products and indicates on the UBQ that she experienced bleeding during the Final Month, the MBL volume will be imputed per the procedure described in Section 8.1.7.1.2.

The primary endpoint will be analyzed using a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate.

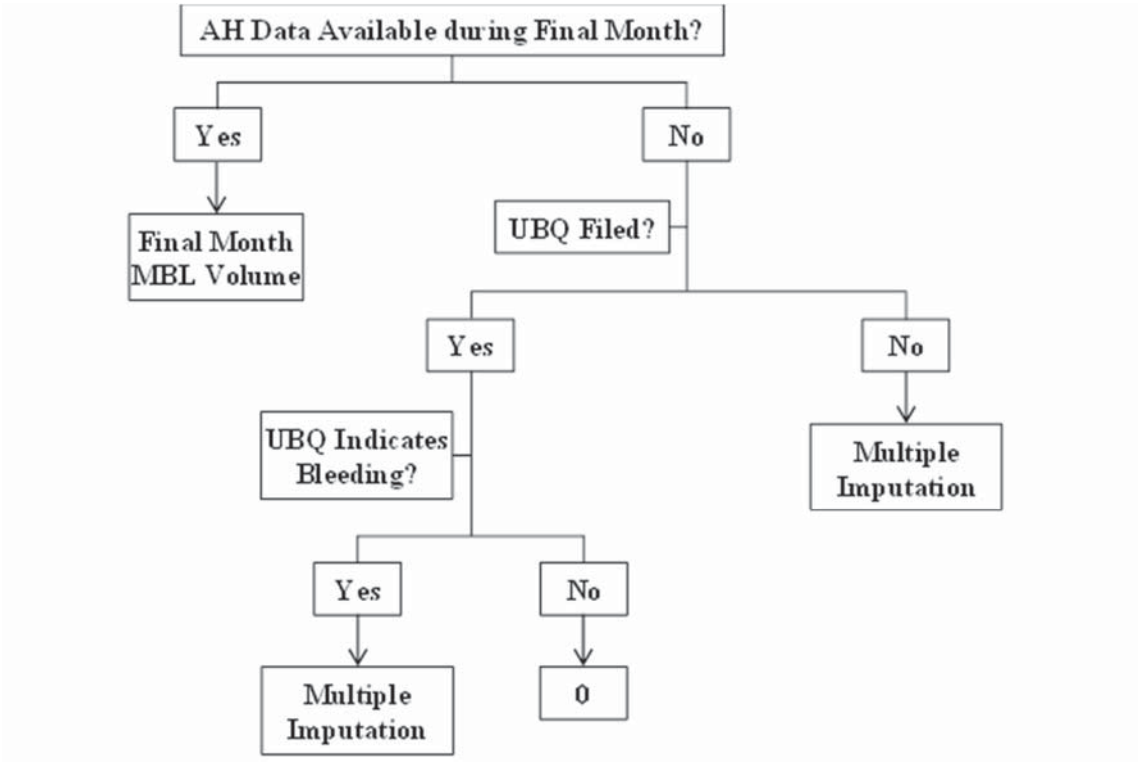
8.1.7.1.2 Derivation of Primary Efficacy Endpoint

The Final Month MBL volume will be derived as follows:

- If a subject has any AH data reported during the Final Month (i.e., she has at least 1 day of AH data during the last 28 days of treatment), then her primary endpoint will be based on AH data during the Final Month. The subject's Final Month MBL volume will be the total MBL volume which is the sum of the observed MBL volume over the last 28 days of treatment.
- If a subject is missing the Final Month AH data and the Uterine Bleeding Questionnaire is completed, then:
- A value of 0 will be assigned to the Final Month MBL volume if no bleeding or spotting, "Subject only had spotting that did not require the use of sanitary products" or "There was no visible blood on the sanitary products" is indicated on the Uterine Bleeding Questionnaire (Appendix G).
- Otherwise, the primary endpoint will be imputed using multiple imputation as described in Section 8.1.7.1.3.

A flow-chart showing how the primary endpoint will be derived is presented in Figure 7.

Figure 7. Flow-Chart for Deriving Primary Endpoint



8.1.7.1.3 Multiple Imputation

The imputation model will include but is not limited to the following variables: baseline MBL volume, treatment group, and 28-day MBL volume at each post-baseline treatment cycle. The final imputation model will be specified in the SAP.

First, *M* "semi-complete" datasets will be imputed to produce monotone missing data via MCMC using SAS PROC MI. Then, *M* "complete" datasets for the Final Month MBL volume will be generated based on each "semi-complete" dataset via linear regression using SAS PROC MI. *M* represents the number of imputed datasets and its value will be specified in the SAP.

Each subject's responder status will be derived based on the imputed Final Month MBL volume from the *M* imputed datasets. And the percentages of responders are analyzed using a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate.

8.1.7.1.4 Sensitivity Analysis of the Primary Efficacy Variable

The sensitivity analyses for the primary endpoint will use different approaches for handling prematurely discontinued subjects and different approaches for dealing with missing Final Month MBL volume. The details of the sensitivity analyses will be specified in the SAP.

Unless otherwise specified, the analysis dataset used for sensitivity analysis is the mITT analysis set.

8.1.7.2 Secondary Efficacy Variables

Ranked secondary efficacy measures during the Treatment Period include the following (the order of the ranked secondary efficacy endpoints will be specified in the SAP):

- Change from baseline in MBL volume to the Final Month;
- Monthly change from baseline in MBL volume;
- Percentage of subjects with suppression of bleeding (no bleeding allowed, spotting allowed) at the Final Month;
- Percentage of subjects with baseline hemoglobin ≤ 10.5 g/dL who have an increase in hemoglobin > 2 g/dL at Month 6.

Non-ranked secondary efficacy measures during the Treatment Period include the following:

- Change and percent change from baseline in MBL volume;
- Percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline during 28-day intervals throughout the Treatment Period;

- Change from baseline in total number of sanitary products used;
- Change and percent change from baseline in hemoglobin concentration;
- PGIC for Menstrual Bleeding and Non-Bleeding Uterine Fibroid Symptoms;
- Change and percent change from baseline in fibroid and uterine volume;
- Change from baseline for the UFS-QoL;
- Change from baseline for the EuroQoL-5D (EQ-5D-5L);
- The HCRU;
- Change from baseline for the WPAI.

Statistical Analyses for Secondary Efficacy Variables

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

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

For the ranked secondary variables, a fixed-sequence approach will be applied to maintain the family-wise type I error rate.

Analysis details will be specified in the SAP.

8.1.7.2.1 Reduction of Bleeding

The percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline during the Treatment Period will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group. Also, the individual component (the percentage of subjects with MBL volume of

< 80 mL as well as the percentage of subjects with ≥ 50% in MBL volume reduction from baseline) will be summarized.

The change and percent change from baseline in MBL volume to each month and to the Final Month, will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

The percentage of subjects with suppression of bleeding and the percentage of subjects with amenorrhea will be summarized by monthly intervals throughout the Treatment Period. For each subject, suppression of bleeding will be defined as having no days of bleeding (spotting is allowed) during a 28-day interval. Amenorrhea is defined as having no days of bleeding or spotting during a 28-day interval. In addition, the cumulative percentage of subjects with suppression of bleeding and the cumulative percentage of subjects with amenorrhea will be compared between each elagolix treatment group and the placebo group.

The change and percent change from baseline to monthly intervals in number of bleeding days will be summarized by treatment group. In addition, the change from baseline in total number of sanitary products will be summarized and compared between each elagolix treatment group and the placebo group.

8.1.7.2.2 Hemoglobin Concentration

The change and percent change from baseline in hemoglobin concentration will be summarized monthly for each treatment group and compared between each elagolix treatment group and the placebo group. Shift tables from baseline to values over time will be summarized by anemia status.

8.1.7.2.3 Fibroid and Uterine Volume

The change and percent change from baseline in primary fibroid volume, total fibroid volume and uterine volume will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

The percentage of subjects with ≥ 25% reduction in total and primary fibroid volume and uterine volume will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

8.1.7.2.4 Quality of Life

UFS-QoL

Improvement in quality of life will be assessed on the UFS-QoL Questionnaire (4-week recall). The change from baseline 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 UFS-QoL total.

EQ-5D-5L

The number and percentage of subjects with answers in each level for Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression will be summarized by treatment group.

The change from baseline in subject health status will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

8.1.7.2.5 Patient Global Impression of Change (PGIC)

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 by treatment group.

PGIC for Non-Bleeding Uterine Fibroid Symptoms (PGIC-NBUFS):

PGIC-NBUFS is to assess the severity of overall non-bleeding symptoms and the severity of specific non-bleeding uterine fibroid symptoms. The number and percentage of

subjects in each response category of each question based on PGIC-NBUFS will be summarized by treatment group.

8.1.7.2.6 Work Productivity and Activity Questionnaire (WPAI)

The change from baseline for the WPAI will be summarized for each treatment group and compared between each elagolix treatment group and the placebo group.

8.1.7.2.7 Health Care Resource Utilization Questionnaire (HCRU)

HCRU will be summarized for each treatment group.

8.1.7.2.8 Multiple Comparisons

The primary efficacy comparison will be between the elagolix 300 mg BID plus E2/NETA group and the placebo group. The comparison between the elagolix 300 mg BID alone group and the placebo group will be used as a reference and to examine the validity of the study design. Therefore, no multiplicity adjustment is necessary. The order of ranked secondary endpoints will be specified in the SAP.

8.1.8 Safety

8.1.8.1 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 unless otherwise specified.

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 unless otherwise specified.

Missing safety data will not be imputed.

Analysis details will be specified in the SAP.

8.1.8.2 Adverse Events

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

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 event
- By system organ class, and preferred term
- By system organ class, preferred term and maximum relationship
- By system organ class, preferred term and maximum severity

- Any event and by system organ class and preferred term for events resulting in study drug discontinuation
- Any event and by system organ class and preferred term for serious events
- Any event and preferred term for AESI's (e.g., hypoestrogenic adverse events)

The Post-Treatment AEs will be summarized in a similar manner as the TEAEs described above.

8.1.8.3 Analysis of Laboratory Data and Vital Signs

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

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

Analysis details will be specified in the SAP.

8.1.8.4 Bone Mineral Density

The within-group percent change from baseline to Month 6 in BMD will be summarized for each treatment group with mean, standard deviation, median and two-sided 95% confidence interval. The between-group differences in percent change from baseline to Month 6 in BMD will be summarized with mean and standard error. The percent change from baseline to Month 6 in BMD will be compared between each elagolix treatment group and the placebo group as well as between the elagolix 300 mg BID group and the elagolix 300 mg BID plus E2/NETA group using ANCOVA with treatment as the main effect and baseline BMD as a covariate. Two-sided 95% confidence intervals will be constructed for the between-group differences in percent change from baseline to Month 6 in BMD.

The number and percentage of subjects with categorized percent change from baseline in BMD (e.g., ≤ –3%, ≤ –5%, or ≤ –8%) will be summarized for each treatment group and comparison between each elagolix treatment group and the placebo group as well as between the elagolix 300 mg BID group and the elagolix 300 mg BID plus E2/NETA group will be made.

In addition, to evaluate BMD change, the percent change from baseline to Month 6 in the Treatment Period using aggregated data from two pivotal studies (Studies M12-815 and M12-817) will be compared between each elagolix treatment group and the placebo group as well as between the elagolix 300 mg BID group and the elagolix 300 mg BID plus E2/NETA group using ANCOVA with treatment as the main effect and baseline BMD as a covariate. Two-sided 95% confidence intervals will be constructed for the differences in percent change from baseline to Month 6 in BMD.

Analysis details will be specified in the SAP.

8.1.8.5 Post-Treatment Analysis of Menstruation

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

8.1.8.6 Endometrial Biopsy

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

8.1.8.7 Pelvic Ultrasound

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 for each treatment group at each time point. The change from baseline to Month 6 in endometrial thickness will be summarized for each treatment group.

8.1.8.8 Columbia Suicide Severity Rating Scale (C-SSRS)

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

8.1.9 Pharmacokinetic/Pharmacodynamic Analysis

Plasma concentrations of elagolix and norethindrone and serum concentrations of estradiol, progesterone, luteinizing hormone and follicle stimulating hormone 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 and progesterone concentrations, versus efficacy and safety. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

Approximately 400 subjects will be randomized in a 1:1:2 ratio to placebo (N = 100), elagolix 300 mg BID (N = 100), or elagolix 300 mg BID plus E2/NETA (N = 200). The sample size will provide at least 90% power to detect a difference between the elagolix 300 mg BID plus E2/NETA group and the placebo group in the percentage of subjects with MBL volume < 80 mL during the Final Month (the last 28 days of treatment) and 50% or greater reduction in MBL volume from baseline to the Final Month under the assumption of responder rates being 60% and 30% for elagolix 300 mg BID plus E2/NETA and placebo, respectively. The sample size determination is primarily driven by the need for a sufficient number of patients for the safety database. The above sample size was calculated using nQuery advisor 7.0.

9.0 Ethics

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

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

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related 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.

Pharmacogenetic samples (DNA and RNA) will only be collected if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic

media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

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

10.2 Case Report Forms

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

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

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

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Patient reported data must be completed for each subject screened/enrolled in this study and entered into the eCRFs.

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

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

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

PK and PD 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 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

All information concerning elagolix and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of elagolix. This information may be disclosed as deemed necessary by AbbVie to other clinical

investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

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

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

Any pharmacogenetic research that may be done using DNA and RNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the Investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic 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 pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

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

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

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report.

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 3 Study to Evaluate the Efficacy and 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:	25 September 2017

Signature of Principal Investigator	Date
Name of Principal Investigator (printed or typed)	

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
		Global Drug Supply Management
		Clinical Operations
		Clinical Pharmacokinetics
		Bioanalysis
		Clinical Development
		Statistics

Appendix C. Study Activities – Washout, Screening and Treatment Periods and Post-Treatment Follow-Up Period

Procedure	Washout (If Applicable) and Screening Period			Treatment Period[a]									
	Washout Period	Screen Visit	Cycle 1 – 3[‡] PCV[b]	Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[b,d]	Unsch Visit	PD (if appl)
Informed Consent	X	X*											
Medical/Social History	X	X*		X[e]									
Gynecological/Obstetrical and Uterine Fibroid History	X	X*		X[e]									
Gynecological (External Genitalia, Pelvic and Breast) Examination[f]		X								X			X
Pap Test		X											
Endometrial Biopsy		X[g]								X[g,%,&]			X[g,h]
Complete Physical Examination; Height (H); Weight (W)	X (H, W)	X* (H, W)		X[e] (W)						X (W)			X (W)
Symptom-Directed Physical Examination		X*			X	X	X	X	X				
Vital Signs (Temp, BP, Pulse, RR)	X	X	X	X[e]	X	X	X	X	X	X	X		X
12-Lead Electrocardiogram (ECG)		X								X			X
Mammogram		X[∞]											
Pelvic Ultrasound[@]: TAU, TVU	X[l]	X*		X			X			X[%,&]			X[h]
Saline Infusion Sonohysterography[@] (SIS)		X[g]											
MRI (Subset of Subjects)[@]		X[j,k]		X[k]						X[%]			X[h]
DXA Scan		X								X[%,±]			X[i]
Dispense Sanitary Products and Collection Kit		X	X	X	X	X	X	X	X	X^	X		X

Procedure	Washout (If Applicable) and Screening Period			Treatment Period[a]									
	Washout Period	Screen Visit	Cycle 1 – 3‡ PCV[b]	Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[b,d]	Unsch Visit	PD (if appl)
(Keg, Collection Bags, etc.)													
Collect and return Sanitary Products; draw venous blood sample			X	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X		X
Clinical Safety Labs: Chemistry, Lipid Panel and Hematology		X		X[e]	X	X	X	X	X	X			X
Clinical Safety Labs: Creatinine Phosphokinase		X		X			X			X			X
Clinical Safety Labs: Urinalysis		X		X[e]			X			X			X
Apolipoprotein A and B				X[e]			X			X			X
Serology (Hepatitis and HIV Screens)		X											
Endocrine: FSH and LH		X[n]		X[e]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]			X[o]
Endocrine: Reflexive TSH and thyroxine-binding globulin (TBG)		X								X[o,p]			X[o,p]
Pharmacodynamic Sample: Serum Estradiol (E2) and Progesterone (P)				X[e]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]			X[o]
Pharmacokinetic Sample (PK): Elagolix and NETA Plasma Concentration				X[q]	X[o]	X[o]	X[o]	X[o]	X[o]	X[o]			X[o]
Pharmacogenetic DNA Sample (Optional based on Subject consent)				X[o]									

Procedure	Washout (If Applicable) and Screening Period			Treatment Period[a]									
	Washout Period	Screen Visit	Cycle 1 – 3[‡] PCV[b]	Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[b,d]	Unsch Visit	PD (if appl)
Pharmacogenetic RNA Sample (Optional based on Subject consent)				X[o]	X[o]		X[o]			X[o]			X[o]
Urine Pregnancy Tests[r]	X	X[s]	X	X[e]	X	X	X	X	X	X[s]	X		X[s]
Serum Pregnancy Tests		X		X[e]						X			X
Contraception Counseling/Dispense Contraceptives as necessary	X	X	X	X	X	X	X	X	X	X	X		X
Birth Control Attestation				X[e]						X			X

Procedure		Washout (If Applicable) and Screening Period			Treatment Period[a]									
		Washout Period	Screen Visit	Cycle 1 – 3[‡] PCV[b]	Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[b,d]	Unsch Visit	PD (if appl)
PRO Questionnaires	Reason for Study Participation				X[e]									
	EQ-5D-5L				X[e]						X			X
	UFS-QoL				X[e]			X			X			X
	PSQ				X[e]									
	Work Productivity and Activity Questionnaire (WPAI)				X						X			X
	UBQ[t]					X	X	X	X	X	X	X	X	X
	PGIC-MB					X		X			X			X
	PGIC-NBUFS					X		X			X			X
	Health Care Resource Utilization (HCRU)					X	X	X	X	X	X			X
	C-SSRS – Baseline/Screening		X		X[e]									
	C-SSRS – Since Last Visit					X	X	X	X	X	X			X
Randomization					X									
Interactive Response Technology (IRT)		X	X	X[#]	X	X	X	X	X	X	X			X
Drug Dispense					X	X	X	X	X	X	X[u]			
Drug Accountability						X	X	X	X	X	X			X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	Washout (If Applicable) and Screening Period			Treatment Period[a]									
	Washout Period	Screen Visit	Cycle 1 – 3‡ PCV[b]	Day 1[c]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[b,d]	Unsch Visit	PD (if appl)
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X
Delay in Roll-over Into Extension Study												X[v]	

‡ **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. If a Complete Physical Examination was performed in Washout, only a Symptom-Directed Physical Examination will be performed in Screening.

% Recommend performing approximately 15 days prior to Month 6 visit.

± Results required to determine eligibility into the extension study.

& Results required if endometrial biopsy at Month 6 cannot be performed or results are insufficient.

∞ Only in subjects ≥ 39 years of age at the time of randomization, unless the mammogram was performed within 3 months prior to Screening.

^ Sanitary products and Sanitary product collection supplies will be dispensed to subjects who are entering the extension study. Subjects will be instructed to continue collecting sanitary products on days with menstrual bleeding or spotting throughout the Treatment Period of the extension study.

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

Screening Cycle 2 Product Collection Visit will be registered in IRT 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, Visit and Assessment Windows, for allowable visit and assessment-specific windows during the 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. A Product Collection Visit is only necessary if a monthly visit is not scheduled to occur within approximately 5 days after cessation of bleeding or spotting.

e. To either be updated or performed or collected prior to study drug administration.

f. Screening breast examination may be omitted when, based on local or country guidelines, breast examinations are routinely or only conducted by breast specialists.

g. Subject must have a confirmed negative urine pregnancy test within 24 hours prior to the SIS and endometrial biopsy.

h. Not required if subject prematurely discontinued prior to Treatment Month 3, i.e., received < 3 months of study drug.

i. DXA scan is not required if subject prematurely discontinued prior to Treatment Month 3, i.e., received < 3 months of study drug (unless the premature discontinuation was related to BMD decrease or the occurrence of a fracture).

j. Subjects who have SIS images which are unable to fully assess the endometrial cavity, may undergo an MRI for further evaluation in Screening.

k. Subjects in the MRI subset who had an MRI during Screening will not repeat the MRI at Day 1. If the Day 1 MRI cannot be performed within the specified assessment window (Table 1), the MRI should not be performed and the subject will not participate in the MRI Subset.

l. 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.

m. If menstrual bleeding or spotting stops within approximately 5 days of a scheduled monthly visit, subject will return sanitary products at the scheduled monthly visit and a venous blood sample will be obtained. The venous blood sample will be sent with collected products to the Alkaline Hematin laboratory.

n. FSH only.

o. Pharmacodynamic (E2 and P), Endocrine (FSH, LH, TBG), Pharmacokinetic (elagolix and NETA) and Pharmacogenetic (DNA and RNA) samples can be drawn at any time during the visit.

p. TBG only.

q. PK sample on Day 1 collected approximately 1 hour post study drug dosing.

r. 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 conducted as early as possible in the first trimester in order to assess the gestational age and estimated due date. The subject will be discontinued from the study at the point the pregnancy was confirmed.

s. Dispense home pregnancy test kit for subjects to self-administer during the Screening Period, prior to SIS and endometrial biopsy, if applicable, and for the Phone Visits during the Post-Treatment Follow-Up Period.

t. The UBQ is to be completed by Site Staff at a scheduled monthly visit, PCV or Unscheduled Visit only if the subject did not return a sanitary product collection keg at the visit.

u. Subjects may require dispensation of additional study drug kits at the Month 6 visit if results from procedures are not available to determine eligibility into the extension study.

v. Unscheduled Visits: For delays in rollover into the Extension Study (M12-816), refer to Section 5.4.4, Table 6, for further details on assessments to be performed.

Study Activities – 12-Month Post-Treatment Follow-Up Period

	12-Month Post-Treatment Follow-Up Period[a]												PCV	PD[#]
	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6***	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**		
Phone Contact/Phone Visit		X		X	X		X	X		X	X			
Pelvic Ultrasound[@]: TVU, TAU			X[b]			X[b]								X[b]
MRI (Subset of Subjects)[@]			X[b]											X[b]
Complete Physical Examination: including weight (W)						X (W)								X (W)
Symptom Directed Physical Examination	X		X						X			X		
Vital Signs	X		X			X			X			X	X	X
DXA Scan						X[c]						X[c]		X[c]
Clinical Safety Labs: Chemistry, Hematology, Lipid Panel and Urinalysis	X		X			X			X			X[d]		X
Apolipoprotein A and B	X		X			X			X			X		X
Urine Pregnancy Test[e]	X	X[f]	X	X[f]	X[f]	X	X[f]	X[f]	X	X[f]	X[f]	X	X	X
Serum Pregnancy Test												X		X
Return sanitary products for the first menses in Post-Treatment													X[g]	
Contraception Counseling/Dispense Contraceptives[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
PRO Questionnaires / UBQ (as applicable)	Xi	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]
Adverse Event Monitoring	X	X[j]	X	X	X	X	X	X	X	X	X	X	X	X

	12-Month Post-Treatment Follow-Up Period[a]													
	Month 1	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6***	**Month 7**	**Month 8**	**Month 9**	**Month 10**	**Month 11**	**Month 12**	**PCV**	**PD#**
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* Subjects who prematurely discontinue from the Treatment Period prior to the Month 3 Study Visit, i.e., who received < 3 months of study drug, will complete the study at the Post-Treatment Follow-up Month 6 visit.

\# Subjects who prematurely discontinue after the Post-Treatment Month 6 visit, should only complete procedures and assessments which are required for the Post-Treatment Follow-up Month 12 visit.

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

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

b. Not required if performed within 2 months prior to PD or if subject prematurely discontinued prior to Treatment Month 3, i.e., received < 3 months of study drug during the Treatment Period.

c. DXA Scan is not required if subject prematurely discontinued prior to Treatment Month 3, i.e., received < 3 months of study drug during the Treatment Period (unless the premature discontinuation was related to BMD decrease or the occurrence of a fracture).

d. Safety labs at Post-Treatment Follow-up Month 12: Lipid Panel only.

e. 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.

f. Home pregnancy test kit will be self-administered at home by the subject.

g. Subject should return sanitary products within approximately 5 days after cessation of bleeding or spotting from the first menses with full menstrual flow in the Post-Treatment Follow-up Period at a Product Collection Visit or a scheduled site visit. The venous blood sample will be sent with collected products to the Alkaline Hematin laboratory. If the subject misses collecting sanitary products for her first full menses, she will be required to collect sanitary products for her next full menses.

h. Subjects are required to continue the use of two forms of non-hormonal birth control throughout the Post-Treatment Follow-Up Period (After Month 2 in the Post-Treatment Follow-Up Period, provided the subject returned to menses, the subject may begin the use of hormonal contraception in place of non-hormonal birth control).

i. Post-Treatment UBQ will only be completed if Subject has not returned sanitary products for her first full menses in the Post-Treatment Period at the time of the Phone or Site visit. Once a Subject returns sanitary products from her first full menses in the Post-Treatment Follow-up Period, the Post-Treatment UBQ no longer needs to be completed.

j. An adverse event of amenorrhea will be reported for subjects who do not return to menses by the Post-Treatment Follow-up Month 2 Phone Visit and the adverse event will be followed until resolution.

Appendix D. BI-RADS Classification

The BI-RADS assessment categories are:

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

Reference: ACR BI-RADS Atlas Fifth Edition. p. 15-8. Available from: https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/BIRADS/01-Mammography/02--BIRADS-Mammography-Reporting.pdf?la=en.[12]

Appendix E. Reason for Study Participation – SAMPLE

We would like to ask you why you have agreed to participate in this clinical research study. I am participating in this research study because (Please check one):

☐ I would like to avoid surgery (hysterectomy)

☐ I would like to delay surgery (hysterectomy)

☐ I would like to avoid other surgeries or procedures (such as myomectomy or uterine artery embolization)

☐ I would like to delay other surgeries or procedures (such as myomectomy or uterine artery embolization)

☐ I prefer taking medication rather than surgery or procedures until I enter menopause when my symptoms, such as heavy menstrual bleeding, should improve and gradually go away

☐ I would like to get pregnant after participating in the study

☐ I don't know why

☐ I don't want to answer

☐ Other: _____

Appendix F. Physician Surgery Questionnaire Version 1.0 – SAMPLE

Based on this subject's current presentation/profile as it relates to uterine fibroids, is surgery or surgical procedure one of the potential treatment options you would consider?

Yes
No

If yes, which surgery or surgical procedure would you consider? Check all that apply.

Hysterectomy
Myomectomy
Uterine Artery Embolization
Other _____

Appendix G. Uterine Bleeding Questionnaire (UBQ) – Treatment Period – SAMPLE

(To be Completed by Site Staff)

Version 2.0

During site visits in the Treatment Period, subjects who **did not** return a Sanitary Product Collection Keg (for menstrual blood loss analysis) will be asked whether they had any uterine bleeding or spotting since their last study visit.

1. **Did the subject have any bleeding or spotting since her last study visit?**

   ☐ No ☐ Yes

If yes, why were sanitary products not collected/returned? (Please select one response)

☐ Subject only had spotting that did not require the use of sanitary products*

☐ There was no visible blood on sanitary products*

☐ Subject forgot to/did not collect*

☐ Subject/Site discarded the sanitary products*

☐ Subject is still bleeding/spotting; will return when bleeding/spotting complete

☐ Subject collected sanitary products and did not bring them to this visit; will return sanitary products at a later date

☐ Other

* If this response is checked, remind subject to collect and return all used or worn sanitary products with or without visible blood.

Appendix H. Uterine Bleeding Questionnaire (UBQ) – Post-Treatment Follow-Up Period – SAMPLE

(To be Completed by Site Staff)

Version 2.0

Subjects who have not returned sanitary products for their first full menses in the Post-Treatment Period, will be asked at the Post-Treatment Phone and Site Visits whether they had any bleeding or spotting since their last site or phone visit. Once a subject returns sanitary products for a full menses in the Post-Treatment Follow-up Period, this questionnaire no longer needs to be completed.

1. **Did the subject have any bleeding or spotting since her last study visit (Site visit or phone visit)?**

   ☐ **No** ☐ **Yes**

If yes, why were sanitary products not collected/returned? (Please select one response)

- ☐ Subject only had spotting that did not require the use of sanitary products*
- ☐ There was no visible blood on sanitary products*
- ☐ Subject forgot to/did not collect*
- ☐ Subject/Site discarded the sanitary products*
- ☐ Subject is still bleeding/spotting; will return when bleeding/spotting complete
- ☐ Subject collected sanitary products and did not bring them in yet; will return sanitary products at a later date
- ☐ Other

* Subject will be required to collect sanitary products for her next full menses.

Appendix I. Uterine Fibroid Symptom Quality of Life Questionnaire (UFS-QoL) – SAMPLE

Pt. Initials: _____ **Pt. ID: _____**

Date: _____

UTERINE FIBROID SYMPTOM AND HEALTH-RELATED QUALITY OF LIFE QUESTIONNAIRE (UFS-QOL)

Listed below are symptoms experienced by women who have uterine fibroids. Please consider each symptom as it relates to your uterine fibroids or menstrual cycle. Each question asks how much distress you have experienced from each symptom during the previous 4 weeks.[1]

There are no right or wrong answers. Please be sure to answer every question by checking (✓) the most appropriate box. If a question does not apply to you, please mark "not at all" as a response.

During the previous 4 weeks[1], how distressed were you by…	Not at all	A little bit	Some-what	A great deal	A very great deal
1. Heavy bleeding during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. Passing blood clots during your menstrual period	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. Fluctuation in the duration of your menstrual period compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Fluctuation in the length of your monthly cycle compared to your previous cycles	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Feeling tightness or pressure in your pelvic area	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Frequent urination during the daytime hours	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Frequent nighttime urination	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Feeling fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

[1] This questionnaire has been modified by AbbVie with the permission of the SIR Foundation. Specifically, rather than asking how much distress you have experienced from various symptoms during the past 3 months, this questionnaires focuses on the past 4 weeks. SIR Foundation has not tested and is not responsible for the validity of this modification. AbbVie plans to test the validity of this instrument using phase 2a and phase 2b trial data. Your use of the questionnaire constitutes your agreement to release SIR Foundation from any responsibility for AbbVie's changes to the document.

Appendix J. Patient Global Impression of Change – Menstrual Bleeding (PGIC-MB) SAMPLE

Please answer the following question regarding your **menstrual bleeding:**

Since I started taking study medication, my menstrual bleeding has:

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

Appendix K. Patient Global Impression of Change Non-Bleeding Uterine Fibroid Symptoms (PGIC-NBUFS) – SAMPLE

Thinking about your condition, please answer the following questions regarding your **non-bleeding uterine fibroid symptoms**, that is, any symptom(s) that is present, whether or not you are having your period:

1. Since I started taking study medication, my **abdominal or pelvic pain** has/is

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

2. Since I started taking study medication, my **abdominal or pelvic pressure** has/is

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

3. Since I started taking study medication, my **abdominal or pelvic cramping** has/is

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

☐ Much worse
☐ Very much worse

4. Since I started taking study medication, my **back pain** has/is

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

5. Since I started taking study medication, my **abdominal bloating** has/is

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

6. Overall since I started taking study medication, my **non-bleeding symptoms** have/are

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

Appendix L. Work Productivity and Activity Impairment Questionnaire: Uterine Fibroids V2.0 (WPAI:UF) – SAMPLE

The following questions ask about the effect of uterine fibroid symptoms on your ability to work and perform regular activities. Please fill in the blanks or circle a number, as indicated.

1. Are you currently employed (working for pay)? _____ NO ___ YES

   If *NO*, check *"NO"* and skip to Question 6.

   The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your uterine fibroid symptoms? *Include hours you missed on sick days, times you went in late, left early, etc., because of your uterine fibroid symptoms. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____ HOURS *(If "0," skip to question 6.)*

5. During the past seven days, how much did your uterine fibroid symptoms affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If uterine fibroid symptoms affected your work only a little, choose a low number. Choose a high number if uterine fibroid symptoms affected your work a great deal.

Consider only how much uterine fibroids affected productivity while you were working.

Uterine fibroid symptoms had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Uterine fibroid symptoms completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your uterine fibroid symptoms affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If uterine fibroid symptoms affected your activities only a little, choose a low number. Choose a high number if uterine fibroid symptoms affected your activities a great deal.

Consider only how much uterine fibroid symptoms affected your ability to do your regular daily activities, other than work at a job.

Uterine fibroid symptoms had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Uterine fibroid symptoms completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Appendix M. EurolQol (EQ-5D-5L) – SAMPLE

Figure 1: EQ-5D-5L (UK English sample version)

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

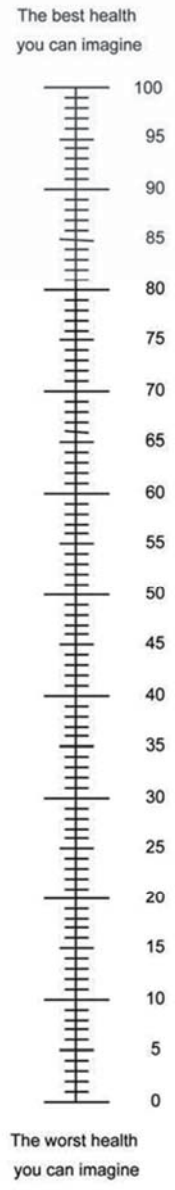
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY= ☐



Appendix N. Columbia-Suicide Severity Rating Scale (C-SSRS) – Baseline/Screening – SAMPLE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

Appendix O. Columbia-Suicide Severity Rating Scale (C-SSRS) – Since Last Visit – SAMPLE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 - 130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:
Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:
Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:
Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:
Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:
Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: ____ _____
Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm,*** just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Appendix P. Health Care Resource Utilization Questionnaire (HCRU) Version 2.0 – SAMPLE

(To be completed by Site Staff)

Non-Study Visits for Routine/General Health Care

Version 2.0

Complete Version 2.0 for Subject's who randomize under Amendment 2

Instructions to Site Staff: At each scheduled monthly visit (Month 1 through Month 6) in the Treatment Period, please ask if the subject saw a ***Non-Study*** Health Care Practitioner (HCP) since her last scheduled monthly visit for a ***routine/general health care visit that is not associated with an adverse event***.

Only record routine/general health care visits with Non-Study HCPs below.

Record Non-Study HCP Visits associated with an adverse event on the Adverse Event form only. Do not record below.

1. Since the Subject's last scheduled monthly study visit, has she seen a non-study Health Care Practitioner (e.g., Physician, Nurse Practitioner, Physician Assistant, Dentist, Physical Therapist) for a **routine/general health care visit that is not associated with an adverse event**? ☐ **No** ☐ **Yes**

If **Yes**, please complete the questions below.

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
☐ Office		☐ AUDIOLOGIST	
		☐ ALLERGIST	
		☐ CARDIOLOGIST	
		☐ DENTIST	
		☐ DERMATOLOGIST	
		☐ ENDOCRINOLOGIST	
		☐ ENT	
		☐ FAMILY PHYSICIAN	
		☐ GASTROENTEROLOGIST	
		☐ GYNECOLOGIST	
		☐ HEMATOLOGIST	
		☐ HEPATOLOGIST	
		☐ IMMUNOLOGIST	
		☐ INFECTIOUS DISEASE SPECIALIST	
		☐ INTERNAL MEDICINE SPECIALIST	
		☐ INTERNIST	
		☐ MEDICAL GENETICIST	
		☐ NEPHROLOGIST	
		☐ NEUROSURGEON	
		☐ NURSE	
		☐ NURSE PRACTITIONER	
		☐ OCCUPATIONAL THERAPIST	
		☐ OPHTHALMOLOGIST	

		☐ ORTHOPEDIC SURGEON	
		☐ OPTOMETRIST	
		☐ PHYSIATRIST	
		☐ PHYSICAL THERAPIST	
		☐ PLASTIC SURGEON	
		☐ PODIATRIST	
		☐ PSYCHOLOGIST	
		☐ PULMONOLOGIST	
		☐ RADIOLOGIST	
		☐ REPRODUCTIVE ENDOCRINOLOGIST	
		☐ RHEUMATOLOGIST	
		☐ SURGEON	
		☐ UROLOGIST	
		☐ UNKNOWN	
		☐ OTHER HEALTH CARE PRACTITIONER (specify type):	
☐ Urgent Care		☐ AUDIOLOGIST	
		☐ ALLERGIST	
		☐ CARDIOLOGIST	
		☐ DENTIST	
		☐ DERMATOLOGIST	
		☐ ENDOCRINOLOGIST	
		☐ ENT	
		☐ FAMILY PHYSICIAN	
		☐ GASTROENTEROLOGIST	
		☐ GYNECOLOGIST	
		☐ HEMATOLOGIST	
		☐ HEPATOLOGIST	

		☐ IMMUNOLOGIST	
		☐ INFECTIOUS DISEASE SPECIALIST	
		☐ INTERNAL MEDICINE SPECIALIST	
		☐ INTERNIST	
		☐ MEDICAL GENETICIST	
		☐ NEPHROLOGIST	
		☐ NEUROSURGEON	
		☐ NURSE	
		☐ NURSE PRACTITIONER	
		☐ OCCUPATIONAL THERAPIST	
		☐ OPHTHALMOLOGIST	
		☐ ORTHOPEDIC SURGEON	
		☐ OPTOMETRIST	
		☐ PHYSIATRIST	
		☐ PHYSICAL THERAPIST	
		☐ PLASTIC SURGEON	
		☐ PODIATRIST	
		☐ PSYCHOLOGIST	
		☐ PULMONOLOGIST	
		☐ RADIOLOGIST	
		☐ REPRODUCTIVE ENDOCRINOLOGIST	
		☐ RHEUMATOLOGIST	
		☐ SURGEON	
		☐ UROLOGIST	
		☐ UNKNOWN	
		☐ OTHER HEALTH CARE PRACTITIONER (specify type):	
☐ Emergency Room		☐ AUDIOLOGIST	

		☐ ALLERGIST	
		☐ CARDIOLOGIST	
		☐ DENTIST	
		☐ DERMATOLOGIST	
		☐ ENDOCRINOLOGIST	
		☐ ENT	
		☐ FAMILY PHYSICIAN	
		☐ GASTROENTEROLOGIST	
		☐ GYNECOLOGIST	
		☐ HEMATOLOGIST	
		☐ HEPATOLOGIST	
		☐ IMMUNOLOGIST	
		☐ INFECTIOUS DISEASE SPECIALIST	
		☐ INTERNAL MEDICINE SPECIALIST	
		☐ INTERNIST	
		☐ MEDICAL GENETICIST	
		☐ NEPHROLOGIST	
		☐ NEUROSURGEON	
		☐ NURSE	
		☐ NURSE PRACTITIONER	
		☐ OCCUPATIONAL THERAPIST	
		☐ OPHTHALMOLOGIST	
		☐ ORTHOPEDIC SURGEON	
		☐ OPTOMETRIST	
		☐ PHYSIATRIST	
		☐ PHYSICAL THERAPIST	
		☐ PLASTIC SURGEON	

		☐ PODIATRIST	
		☐ PSYCHOLOGIST	
		☐ PULMONOLOGIST	
		☐ RADIOLOGIST	
		☐ REPRODUCTIVE ENDOCRINOLOGIST	
		☐ RHEUMATOLOGIST	
		☐ SURGEON	
		☐ UROLOGIST	
		☐ UNKNOWN	
		☐ OTHER HEALTH CARE PRACTITIONER (specify type):	

6. Did the Subject have any diagnostic or therapeutic procedures performed since the last scheduled monthly study visit? ☐ No ☐ Yes (If Yes, complete questions 7 and 8 below)

7. Diagnostic/Therapeutic Procedure (Check all that apply)		**8. How many times was the procedure performed?**
Ultrasound Scan	☐	
Physical Examination	☐	
Vital Signs	☐	
MRI	☐	
CT Scan	☐	
X-Ray	☐	
Biopsy and Histologic Examination	☐	
Pelvic Exam	☐	
Urine Test	☐	
Blood Test	☐	
Other (specify):_____	☐	

Appendix Q. Health Care Resource Utilization Questionnaire (HCRU) Version 1.0 – SAMPLE

(To be completed by Site Staff)

Non-Study Visits for Routine/General Health Care

Complete Version 1.0 for Subjects who randomized under Amendment 1

Instructions to Site Staff: At each scheduled monthly visit in the Treatment Period, please ask if the subject saw a ***Non-Study*** Health Care Practitioner (HCP) since her last scheduled monthly visit for a ***routine/general health care visit that is not associated with an adverse event***.

Only record routine/general health care visits with Non-Study HCPs below.

Record Non-Study HCP Visits associated with an adverse event on the Adverse Event form only. Do not record below.

1. Since the Subject's last scheduled monthly study visit, has she seen a ***non-study*** Health Care Practitioner (e.g., Physician, Nurse Practitioner, Physician Assistant, Dentist, Physical Therapist) for a **routine/general health care visit**? ☐ **No** ☐ **Yes**

If **Yes**, please complete questions 2 and 3 below to indicate the type(s) of *Non-Study Physician(s)* seen and the number of times each Non-Study Physician was seen.

2. What type(s) of *Non-Study* Physician Specialty was the Subject seen by? (Check all that apply)		**3. How many times was the subject seen by each *Non-Study* HCP**
AUDIOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
ALLERGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
CARDIOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
DENTIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
DERMATOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
ENDOCRINOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
ENT	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
FAMILY PRACTITIONER	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
GASTROENTEROLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
GYNECOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
HEMATOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
HEPATOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
IMMUNOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
INFECTIOUS DISEASE SPECIALIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
INTERNAL MEDICINE SPECIALIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
INTERNIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
MEDICAL GENETICIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
NEPHROLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
NEUROSURGEON	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
OPTHAMOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
ORTHOPEDIC SURGEON	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
PHYSIATRIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
PLASTIC SURGEON	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
PODIATRIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
PSYCHIATRIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
PSYCHOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
PULMONOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
RHEUMATOLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
SURGEON	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
UROLOGIST	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
OTHER PHYSICIAN (specify type: _____	☐	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Appendix R. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.2 Synopsis
Subsection Screening Period:
First sentence previously read:

Following informed consent (if Washout was not required), subjects will enter into a 2.5- to 3.5-month Screening Period to establish eligibility based on inclusion and exclusion criteria.

Has been changed to read:

Following informed consent (if Washout was not required), subjects will enter into an approximate 2.5- to 3.5-month Screening Period to establish eligibility based on inclusion and exclusion criteria.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Definition of Terms
"Screening Period," first sentence previously read:

The 2.5 to 3.5 month period prior to randomization on Day 1, when screening procedures are performed to establish eligibility.

Has been changed to read:

The approximate 2.5 to 3.5 month period prior to randomization on Day 1, when screening procedures are performed to establish eligibility.

Section 3.2.3 Pregnancy in Elagolix Studies
Subsection Efficacy in Phase 2 Uterine Fibroid Studies
Fifth paragraph, second sentence previously read:

The study consisted of a 2.5- to 3.5-month Screening Period, a 6-month Treatment Period, and a 6-month Post-Treatment Follow-Up Period.

Has been changed to read:

The study consisted of an approximate 2.5- to 3.5-month Screening Period, a 6-month Treatment Period, and a 6-month Post-Treatment Follow-Up Period.

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

Subjects who do not require washout will enter directly into the 2.5- to 3.5-month Screening Period and will provide written informed consent before any study-related procedures are performed.

Has been changed to read:

Subjects who do not require washout will enter directly into the approximate 2.5- to 3.5-month Screening Period and will provide written informed consent before any study-related procedures are performed.

Section 5.3.1.1 Study Procedures
Fourth paragraph, first sentence previously read:

It is recommended that the Ultrasound, MRI (if applicable), DXA scan and endometrial biopsy for the Month 6 Visit be conducted within approximately 15 days prior to the scheduled Month 6 Visit to allow the results to be available from the central vendors in order to determine eligibility for inclusion into the extension study (Study M12-816).

Has been changed to read:

It is recommended that the pelvic ultrasound, MRI (if applicable), DXA scan and endometrial biopsy for the Month 6 Visit be conducted within approximately 15 days prior to the scheduled Month 6 Visit to ensure the images are received and acceptable for review by the central vendor.

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

During the Treatment and Post-Treatment periods, the ICL may issue a report if any significant changes are observed that may affect subject safety during the study.

Has been changed to read:

The ICL will only issue a report for pelvic ultrasound at Treatment Month 6. A report for all other Treatment and Post-Treatment timepoints for pelvic ultrasound and MRI will only be issued if any significant changes are observed that may affect subject safety during the study.

Section 5.3.1.1 Study Procedures
Subsection Central Imaging Procedures
Last paragraph previously read:

It is recommended that the pelvic ultrasound and MRI (if applicable) performed for the Month 6 Visit are conducted approximately 15 days prior to the scheduled Month 6 Visit to ensure the results are received from the central vendor in order to determine eligibility for inclusion into the extension study. If the results are not available by the Month 6 visit of the Treatment Period, refer to Section 5.4.4 for instructions until results are available to determine eligibility into the extension study.

Has been changed to read:

It is recommended that the pelvic ultrasound and MRI (if applicable) performed for the Month 6 Visit are conducted approximately 15 days prior to the scheduled Month 6 Visit to ensure the images are received and acceptable for review by the central vendor. The central pelvic ultrasound report is only required prior to rollover in the event the Month 6 endometrial biopsy cannot be performed or biopsy results are insufficient. In this case the central pelvic ultrasound is required to determine if the endometrial thickness is ≥ 4 mm in which case the subject needs a repeat biopsy prior to rollover (see Section 5.3.1.1 Endometrial Biopsy). If the results are not available by the Month 6 visit of the Treatment

Period to determine need for a repeat endometrial biopsy, refer to Section 5.4.4 for instructions until results are available to determine eligibility into the extension study.

Section 5.3.1.1 Study Procedures
Subsection Qualifying Uterine Fibroids:
Second paragraph, last bullet previously read:

Multiple small fibroids with a total uterine volume of ≥ 200 cm^3 to ≤ 2,500 cm^3 as documented by centrally read imaging vendor

Has been changed to read:

Multiple fibroids with a total uterine volume of ≥ 200 cm^3 to ≤ 2,500 cm^3 as documented by centrally read imaging vendor

Section 5.4 Removal of Subjects from Therapy or Assessment
Fourth bullet previously read:

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.

Has been changed to read:

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

Section 5.4 Removal of Subjects from Therapy or Assessment
Sixth bullet previously read:

The subject has (SGPT/ALAT) or SGOT/ASAT elevation > 5 times the upper limit of normal confirmed upon repeat.

Has been changed to read:

The subject has (SGPT/ALAT) or SGOT/ASAT elevation > 5 times the upper limit of normal confirmed upon repeat during the Treatment Period.

Section 5.4.4 Delays in Rollover into the Extension Study
First paragraph, second sentence previously read:

Subjects will return to the study site at the same monthly visit intervals.

Has been changed to read:

Subjects will return to the study site at the same 28-day monthly visit intervals if eligibility for the extension study has not been determined before then.

Section 5.4.4 Delays in Rollover into the Extension Study
Subsection <u>Subject Entering the Extension Study:</u>
Delete: third bullet

Conduct the study assessments and procedures as outlined in Table 6, Delays in Roll-Over into Extension Study.

Section 5.4.4 Delays in Rollover into the Extension Study
Subsection <u>Subject NOT Entering the Extension Study:</u>
Delete: third bullet

Conduct the study assessments and procedures as outlined in the Unscheduled Visit procedures above

Section 5.4.4 Delays in Rollover into the Extension Study
Subsection <u>Subject NOT Entering the Extension Study:</u>
Last bullet previously read:

The next scheduled visit will be the Month 1 Phone Visit

Has been changed to read:

The next scheduled visit will be the Month 1 Site Visit

Section 15.0 Reference List
Add: new reference 12

ACR BI-RADS Atlas Fifth Edition. p. 15-8. Available from: https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/BIRADS/01-Mammography/02--BIRADS-Mammography-Reporting.pdf?la=en.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
		Global Drug Supply Management
		Clinical Operations
		Clinical Pharmacokinetics
		Bioanalysis
		Clinical Development
		Statistics

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical Development
		Global Drug Supply Management
		Clinical Operations
		Clinical Pharmacokinetics
		Bioanalysis
		Clinical Development
		Statistics

Appendix C. Study Activities – Washout, Screening and Treatment Periods and Post-Treatment Follow-Up Period Procedure "Endometrial Biopsy," "Pelvic Ultrasound[@]: TAU, TVU," and "DXA Scan" previously read:

	Washout (If Applicable) and Screening Period			Treatment Period[a]									
Procedure	**Washout Period**	**Screen Visit**	**Cycle 1 – 3[‡] PCV[b]**	**Day 1[c]**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**PCV[b,d]**	**Unsch Visit**	**PD (if appl)**
Endometrial Biopsy		X[g]								X[g,%]			X[g,h]
Pelvic Ultrasound[@]: TAU, TVU	X[l]	X*		X			X			X[%]			X[h]
DXA Scan		X								X[%]			X[i]

Has been changed to read:

	Washout (If Applicable) and Screening Period			Treatment Period[a]									
Procedure	**Washout Period**	**Screen Visit**	**Cycle 1 – 3[‡] PCV[b]**	**Day 1[c]**	**Month 1**	**Month 2**	**Month 3**	**Month 4**	**Month 5**	**Month 6**	**PCV[b,d]**	**Unsch Visit**	**PD (if appl)**
Endometrial Biopsy		X[g]								X[g,%,&]			X[g,h]
Pelvic Ultrasound[@]: TAU, TVU	X[l]	X*		X			X			X[%,&]			X[h]
DXA Scan		X								X[%,±]			X[i]

Appendix C. Study Activities – Washout, Screening and Treatment Periods and Post-Treatment Follow-Up Period
Table note "%" previously read:

Recommend performing approximately 15 days prior to Month 6 visit to ensure results are available to determine eligibility into the extension study.

Has been changed to read:

% Recommend performing approximately 15 days prior to Month 6 visit.
± Results required to determine eligibility into the extension study.
& Results required if endometrial biopsy at Month 6 cannot be performed or results are insufficient.

Appendix D. BI-RADS Classification
Previously read:

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

Has been changed to read:

The BI-RADS assessment categories are:

- 0 – Incomplete,
- 1 – Negative,
- 2 – Benign,
- 3 – Probably benign,
- 4 – Suspicious,

- 5 – Highly suggestive of malignancy,
- 6 – Known biopsy – proven malignancy

Reference: ACR BI-RADS Atlas Fifth Edition. p. 15-8. Available from: https://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/BIRADS/01-Mammography/02--BIRADS-Mammography-Reporting.pdf?la=en.[12]