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Protocol for Study M16-824

Safety and Efficacy of Elagolix for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

VERSION:	4.0	DATE:	12 June 2020
SPONSOR:	AbbVie Inc.*	NUMBER OF SITES:	Approximately 45
ABBVIE INVESTIGATIONAL PRODUCT:	Elagolix (ABT-620)		

FULL TITLE: A Phase 4 Study to Evaluate the Safety and Efficacy of Elagolix for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

Incorporating Versions 1.0, 2.0, 3.0, and 4.0 and Administrative Change 1.

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: A Phase 4 Study to Evaluate the Safety and Efficacy of Elagolix for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women	
Background and Rationale:	Results for Phase 2 and 3 studies in subjects with uterine fibroids indicate that elagolix reduces heavy menstrual bleeding (HMB). Elagolix 150 mg once daily (QD) provides a dosage option for premenopausal women not suitable for or prefer not to receive hormonal add-back therapy and/or desire an option of once a day dosing for HMB with uterine fibroids.
Objective(s) and Endpoint(s):	Objective To assess the safety and efficacy of elagolix 150 mg QD compared to placebo in reducing HMB associated with uterine fibroids in premenopausal women. The primary hypothesis is that elagolix 150 mg QD, compared to placebo, reduces HMB associated with uterine fibroids in premenopausal women. Primary Endpoint The primary endpoint will be the proportion of subjects meeting the following conditions: • Menstrual blood loss (MBL) volume < 80 mL at the Final Month (the last 28 days of treatment), and • ≥ 50% reduction in MBL volume from Baseline to the Final Month (the last 28 days of treatment). Pharmacokinetic (PK) endpoint: Exposures of elagolix will be summarized, and elagolix concentrations may be combined with other studies and used to develop a population PK model. Pharmacodynamic endpoint: Concentrations of estradiol will be obtained at designated visits throughout the study and summarized. Estradiol data may be combined with data from other studies and used for exposure-response analysis. The safety endpoints will be based on the following evaluations: physical examination, vital signs measurements, electrocardiogram (ECG) variables, clinical laboratory testing (including hematology, chemistry, urinalysis, and lipid panel), and adverse event (AE) monitoring.
Investigator(s):	Multicenter
Study Site(s):	Approximately 45 sites (Unites States, including Puerto Rico)
Study Population and Number of Subjects to be Enrolled:	Approximately 48 premenopausal women 18 to 51 years of age with HMB and uterine fibroids
Investigational Plan:	This is a Phase 4 randomized, double-blind, 6-month placebo-controlled, parallel-group, multicenter study. Premenopausal women 18 to 51 years of age with HMB associated with uterine fibroids will be selected for this study.

	Once eligibility is established during the Screening Period, eligible subjects will be randomly assigned in the double-blind period at the baseline visit to receive either elagolix 150 mg QD or placebo in a 2:1 ratio for 6 months. Following the double-blind Treatment Period, there will be a 1-month Post-Treatment Follow-Up (PTFU) Period.
Key Eligibility Criteria:	Premenopausal women 18 to 51 years of age at the time of screening with documented uterine fibroids (pelvic ultrasound) and HMB (MBL > 80 mL during 1 menses in Screening).
Study Drug and Duration of Treatment:	Elagolix 150 mg or matching placebo tablets are to be taken daily in the morning for up to 6 months.
Date of Protocol Synopsis:	12 June 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

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 (US).[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 US.[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] The most common symptom and the most common reason for hysterectomy in women with uterine fibroids is heavy or prolonged menstrual bleeding. Non-bleeding symptoms, such as pelvic pain, are also a common reason for hysterectomy.

While there are numerous surgical options available to manage heavy bleeding or other symptoms due to uterine fibroids, until recently there was no Food and Drug Administration (FDA)-approved long-term medical treatment for symptomatic uterine fibroids.

Elagolix sodium (hereinafter "elagolix," also referred to as ABT-620) is a novel, oral, short-acting, nonpeptide, gonadotropin-releasing hormone (GnRH) antagonist that competitively inhibits the GnRH receptors in the pituitary gland. Elagolix, unlike injectable GnRH analogs, produces a dose-dependent suppression of pituitary and ovarian hormone levels in women, i.e., from partial ovarian suppression at lower doses to nearly full suppression at higher doses. To support long-term therapy with elagolix at higher doses, hormonal add-back therapy would be required to mitigate changes in bone mineral density (BMD) and minimize other hypoestrogenic adverse effects of estradiol (E2) suppression (e.g., hot flush). A detailed discussion of the preclinical toxicology, metabolism, pharmacology, and pharmacokinetics (PK) of elagolix in humans and a summary of clinical studies can be found in the Investigator's Brochure.[6]

This study is being conducted to provide an option of elagolix 150 mg once daily (QD) for premenopausal women with HMB associated with uterine fibroids who are not suitable for or prefer not to use hormonal add-back therapy and/or desire an option of once a day dosing.

Clinical Hypothesis

Elagolix 150 mg QD will be effective in reducing HMB compared to placebo in premenopausal women with uterine fibroids.

2.2 Benefits and Risks to Subjects

Elagolix (Oriahnn®) capsules 300 mg with 1.0 mg E2 and 0.5 mg Norethindrone acetate (NETA) has been approved by the US FDA on 29 May 2020 for the management of HMB associated with uterine fibroids.

Completed Phase 2 studies and preliminary results from the Phase 3 studies of elagolix for the management of HMB associated with uterine fibroids show reduction in HMB in women with uterine fibroids compared with placebo. The overall safety profile from Phase 2 showed elagolix is well tolerated. Safety results for the Phase 3 studies in uterine fibroids are consistent with the Phase 2 safety results. Elagolix 150 mg is approved for the management of moderate to severe pain associated with endometriosis.[7] Thus, the benefit/risk profile for the study is favorable.

For further details, please see findings from completed studies, including safety data in the elagolix Investigator's Brochure.[6]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

To assess the safety and efficacy of elagolix 150 mg QD compared to placebo in reducing HMB associated with uterine fibroids in premenopausal women. The primary hypothesis is that elagolix 150 mg QD, compared to placebo, reduces HMB associated with uterine fibroids in premenopausal women.

3.2 Primary Endpoint

The primary endpoint will be the proportion of subjects meeting the following conditions:

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

3.3 Additional Endpoints

- Proportion of subjects with suppression of bleeding at the Final Month and each month during the Treatment Period
- Proportion of subjects with amenorrhea at the Final Month and each month during the Treatment Period
- Change and percent change from Baseline in MBL volume at the Final Month and each month during the Treatment Period
- Change and percent change from Baseline in hemoglobin concentration at each month during the Treatment Period
- Patient Global Impression of Change – Menstrual Bleeding (PGIC-MB) at each month during the Treatment Period
- Change from Baseline in Uterine Fibroid Symptoms Quality of Life (UFS-QoL) at each scheduled assessment

3.4 Safety Endpoints

The safety endpoints will be based on the following evaluations: physical examinations, vital signs measurements, electrocardiogram (ECG) variables, clinical laboratory testing (including hematology, chemistry, urinalysis, and lipid panel), and adverse event (AE) monitoring.

3.5 Pharmacokinetic and Pharmacodynamic Endpoints

Pharmacokinetic Endpoints

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

Pharmacodynamic Endpoint

Serum E2 concentrations will be determined at designated visits throughout the study and summarized. Additional pharmacodynamic parameters may be calculated if useful in the interpretation of the data. Estradiol data may be combined with data from other studies and used for exposure-response analysis.

3.6 Biomarker Research Samples

Optional samples (whole blood, serum, and plasma) will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The objective of research is to analyze samples for biomarkers that will help in the understanding of uterine fibroids, related conditions, response to treatment with elagolix (or similar compounds), and changes in BMD. Research may also include changes in epigenetics, gene expression, and proteomics that may be associated with uterine fibroids, related conditions, or the subject's response to treatment. This research is exploratory in nature and the results may not be included with the clinical study report. Biomarker samples will be collected only from subjects who consent to the optional exploratory analyses, unless precluded by local regulations or restrictions.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 4, randomized, double-blind, 6-month placebo-controlled, parallel-group, multicenter study. Premenopausal women 18 to 51 years of age with uterine fibroids and HMB, as evidenced by MBL > 80 mL during 1 menses in Screening as measured by the alkaline hematin method, will be selected for this study. See Section 5.1 for information regarding eligibility criteria.

Once eligibility is established during the Screening Period, eligible subjects will be randomly assigned in the double-blind period at the baseline visit to receive either elagolix 150 mg QD or placebo in a 2:1 ratio for 6 months. Following the double-blind Treatment Period, there will be a 1 month Post-

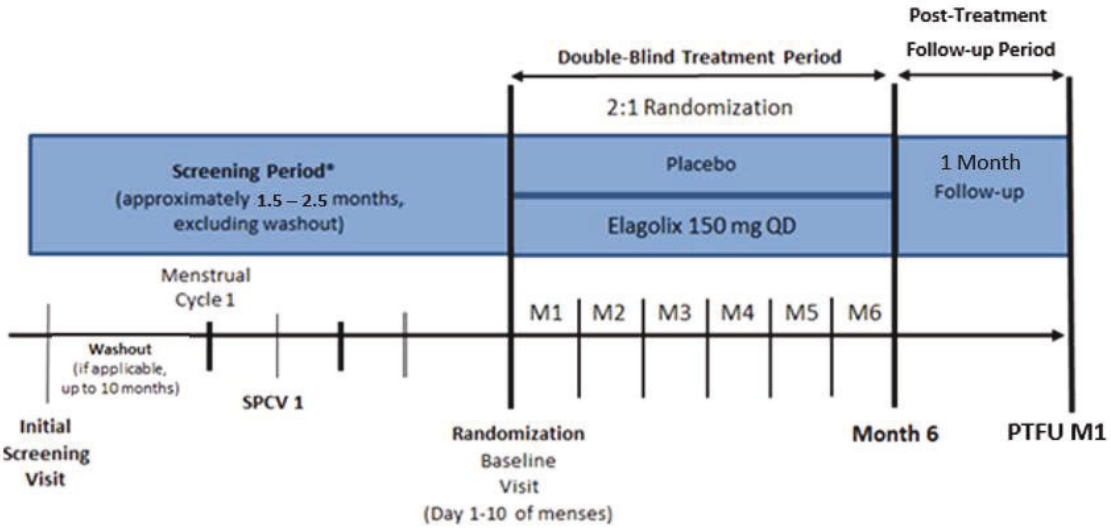
Treatment Follow-Up (PTFU) Period. The study will be conducted in approximately 45 sites in the US (including Puerto Rico).

Total study duration can be up to 9 months (Screening Period of approximately 1.5 to 2.5 months prior to Study Day 1 [Baseline]). The study consists of the following 4 study periods:

- Washout Period: up to 10 months prior to Screening (only applicable if subject is taking exclusionary medication at the time of consent); duration is based on the excluded medication (Table 1).
- Screening Period: approximately 1.5 to 2.5 months prior to Study Day 1 (Baseline). Screening-related procedures to assess for eligibility must be conducted within first 1.5- to 2.5-month duration. However, in the event the cycle or product collection is not complete within 2.5 months during the Screening Period, the Screening Period may be extended with prior approval from AbbVie therapeutic area medical director (TA MD) and would result in a longer duration of participation for the subject than outlined.
- Treatment Period: duration of 6 months (double-blind). For all subjects who meet eligibility criteria during the Screening Period, each subsequent visit during the Treatment Period should be scheduled based on the date of the Day 1 (randomization) visit.
- PTFU Period: One month following the last dose of study drug. All subjects are expected to enter the 1-month PTFU after completing Treatment Month 6 or once a subject prematurely discontinues from the treatment period.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in Appendix F, Operations Manual.

Figure 1. Study M16-824 Schematic



M = month; QD = once daily; PTFU = Post-Treatment Follow-up; SPCV = Screening Product Collection Visit

* The Screening Period may be extended in certain circumstances (e.g., heavy menstrual bleeding < 80 mL) by obtaining sponsor approval.

Rescreening

Subjects who screen fail for this study (Study M16-824) may be rescreened with the TA MD's approval. The TA MD will determine which procedures need to be repeated if the subject was a screen failure for this study. The subject must re-consent and meet all eligibility criteria at the time of re-screening to qualify for the study.

Choice of Control Group

The control group consists of subjects randomly assigned to receive placebo.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All clinical and laboratory procedures in this study are standard and generally accepted.

For efficacy assessments, validated questionnaires will be used to query study subjects about symptoms that occur commonly in patients with uterine fibroids or how uterine fibroids affects daily tasks and activities.

Suitability of Subject Population

Premenopausal women 18 to 51 years of age with uterine fibroids who have HMB (> 80 mL during 1 menses in Screening) are selected for this study. The lower age limit (18 years) was chosen based on the relative paucity of adolescent females with symptomatic uterine fibroids before 18 years of age; the upper age limit (51 years) is included to reduce the risk of subjects becoming menopausal during the study. No studies in females outside of the reproductive years are necessary for this proposed indication.

Selection of Doses in the Study

The dose of elagolix 150 mg QD was selected to provide optimum efficacy while maintaining an acceptable safety profile in women with HMB and uterine fibroids not suitable for or prefer not to receive hormonal add-back therapy and/or desire an option of once a day dosing for HMB with uterine fibroids.

Based on preliminary integrated PK exposure-response analysis for efficacy from Phase 2 studies in women with HMB and uterine fibroids [redacted], elagolix 150 mg QD is predicted to provide clinically meaningful efficacy in reduction of HMB. Elagolix has been evaluated extensively in women with HMB and uterine fibroids in Phase 2 studies. No safety signals were observed in Phase 2a and 2b studies, and safety results from Phase 2 and Phase 3 studies show that elagolix is generally well tolerated. Refer to the elagolix Investigator's Brochure for further details.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subject has voluntarily signed and dated the informed consent form (ICF), approved by an institutional review board (IRB)/independent ethics committee (IEC), prior to washout (if applicable) or initiation of any screening or study-specific procedures.
- 2. Table 1Subject agrees to the washout intervals for hormonal therapies, including any other medication that may require washout (Table 1).
- 3. Subject is not taking exclusionary therapies (Table 2) within the specified washout interval prior to the initiation of any screening procedures.
- 4. Subject must be willing to comply with study-related assessments and procedures and in the judgment the investigator is a suitable candidate for the study.
- 5. Subject must agree to the use of at least 2 forms of non-hormonal contraception (dual contraception) consistently throughout Washout (if applicable), Screening, Treatment, and PTFU Periods.
- 6. Subject should agree to not participating in other investigational trials (drug or device) throughout the study.

Demographics

- 7. Subject is a premenopausal female, 18 to 51 years of age at the time of Screening.
- 8. Criterion has been removed.
- 9. Uterine fibroids documented by a pelvic ultrasound (transabdominal ultrasound [TAU], transvaginal ultrasound [TVU]) assessed by a central reader and verification that a uterine fibroid meets at least one of the following criteria:
  - Intramural, submucosal non-pedunculated fibroid with a diameter ≥ 2 cm (longest diameter)
  - Subserosal fibroid ≥ 4 cm (longest diameter)
  - Multiple fibroids with a total uterine volume of ≥ 200 cm^3 to ≤ 2,500 cm^3
- 10. HMB associated with uterine fibroids as evidenced by MBL > 80 mL during 1 menses in Screening as measured by the alkaline hematin method.

Laboratory Assessments and Other Tests

- 11. Laboratory values must meet the following criteria at Screening (unless otherwise specified):

- Hemoglobin ≥ 7 g/dL (subjects with initial screening hemoglobin results < 7 g/dL can be prescribed iron supplements and have their hemoglobin levels retested prior to Day 1).
- Serum creatinine ≤ 2.0 mg/dL at Screening.
- Aspartate aminotransferase (AST) or alanine transaminase (ALT) < 3 × times the upper limit of the reference range and bilirubin < 2 times the upper limit of the reference range (unless known diagnosis of Gilbert's disease).
- Screening follicle-stimulating hormone (FSH) level of < 35 mIU/mL (35 IU/L).
- Negative urine and/or serum pregnancy test(s) during the Washout (if applicable) and/or Screening Periods, and a negative urine pregnancy test immediately before administration of the first dose of study drug.

12. Subjects must not have hepatitis B nor C based on the presence of the following:
    - Hepatitis B surface antigen (HBsAg)
    - Hepatitis C virus antibody (HCV Ab) with reactive ribonucleic acid (RNA) test
13. No clinically significant abnormalities in clinical chemistry, hematology, or urinalysis (excluding findings associated with the disease under study such as low hemoglobin or low hematocrit). Clinically significant laboratory abnormalities may be retested once prior to Day 1. For further retesting, contact the TA MD.
14. An adequate endometrial biopsy performed during screening or final report of endometrial biopsy done within 3 months prior to Screening available for Principal Investigator (PI) review showing no clinically significant endometrial pathology at Screening.
15. Subject ≥ 21 years of age at Screening (or age at which Papanicolaou [Pap] smears are routinely performed according to local or country guidelines) has a Pap smear result that meets eligibility criteria as indicated in Operations Manual Figure 1, Pap Test Eligibility (Operations Manual [Appendix F]) during Screening or within 3 months prior to Screening.
16. Subject ≥ 40 years of age at the time of informed consent has a normal mammogram (Breast Imaging Reporting and Data System [BI-RADS] Classification 1 to 3 or equivalent) during Screening or within 3 months prior to Screening.
17. No clinically significant abnormal ECGs during Screening.

Subject History

18. Menstrual cycles with interval of 24 to 38 days in length for the 3 consecutive months prior to Screening.
19. Must not have clinically significant gynecological finding from screening ultrasound or saline infusion sonohysterography (SIS) or MRI (if SIS is unevaluable), including:
    - 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 to 6 weeks; however, the results must be evaluated prior to Day 1 and meet eligibility criteria.)
    - Complex ovarian cyst > 3.5 cm in diameter at longest point

- An endometrioma > 3.5 cm in diameter (longest diameter)
- Large endometrial polyp (≥ 1 cm)
- Intracavitary submucosal pedunculated fibroid

20. Must not have a myomectomy, uterine artery embolization, or high-intensity focused ultrasound (HIFU) within 6 months prior to Screening or an endometrial ablation within 6 months prior to Screening.
21. Must not have active pelvic inflammatory disease.
22. Must be > 6 months post-partum, post-abortion, post-pregnancy, and post lactation at the time of entry into the Screening Period.
23. Must not be pregnant or breastfeeding or planning a pregnancy until completion of the study.
24. No diagnoses or history of:
    - Hereditary blood coagulation disorder (e.g., Von Willebrand disease, Factor V Leiden).
    - History of surgery-related severe bleeding or severe and prolonged bleeding associated with dental work.
    - Two separate events of blood transfusions within 9 months prior to Screening (with exception of transfusions associated with low hemoglobin or low hematocrit due to uterine fibroids) or blood transfusions within 60 days prior to Day 1.
    - Active malignancy or history of malignancy (except basal cell carcinoma of the skin) with or without systemic chemotherapy.
    - Documented history of a severe, life-threatening, or other significant sensitivity to any drug.
25. No osteoporosis, osteopenia, ***or*** other metabolic bone disease, including:
    - Intercurrent bone disease (e.g., osteomalacia, osteogenesis imperfecta).
    - History or presence of a condition associated with a decrease in BMD (e.g., uncontrolled hyperthyroidism, uncontrolled hyperparathyroidism, anorexia nervosa) or requires chronic treatment with systemic corticosteroids.
    - History of low-trauma bone fractures (e.g., fracture resulting from a fall from a standing height or lower).
    - Bilateral hip replacement.
    - Clinically significant hypocalcemia, hypo- or hyperphosphatemia.
    - Treatment with medication (excluding calcium and vitamin D) for bone disease associated with a decrease in BMD.
26. No history of:
    - A newly diagnosed, clinically significant medical condition requiring therapeutic intervention (e.g., new onset hypertension) that has not been stabilized prior to Day 1.
    - A clinically significant medical condition anticipated to require intervention during the course of the study participation (e.g., anticipated major elective surgery).

- An unstable medical condition making the subject an unsuitable candidate for the study in the opinion of the investigator.
- Any suicide attempts "ever" or subject answers "yes" to questions 4 or 5 on the suicidal ideation portion (referring to within the last year) of the Columbia-Suicide Severity Rating Scale (C-SSRS) when administered during Screening or prior to dosing on Study Day 1.
- Drug abuse and/or alcohol abuse within 12 months prior to Screening.
- Major depression or post-traumatic stress disorder (PTSD) episode within 2 years prior to Screening.
- Other major psychiatric disorders at any time (e.g., schizophrenia, bipolar disorder).

27. No surgical history of:
    - Hysterectomy (with or without oophorectomy)
    - Bilateral oophorectomy
    - Bariatric surgical procedures of any type within 6 months prior to Screening
28. Must not be using:
    - Medications as identified inTable 1 Table 2
    - Copper intrauterine device (CU-IUD)
        - For a subject using a contraceptive sub-dermal implant or CU-IUD:
            - The contraceptive sub-dermal implant must be removed, and subject must complete the Washout per Table 1 and subsequently have 1 menses after completion of Washout.
            - The CU-IUD must be removed and subsequently have 1 menses after completion of Washout.
            - Levonorgestrel intra-uterine system (LNG-IUS) is allowed. If a subject has LNG-IUS in place, the LNG-IUS must be in place for 6 months or longer before the subject will be screened, and the LNG-IUS should remain throughout the Treatment Period and the PTFU Month 1 visit. If a subject does not have LNG-IUS in place at the beginning of Screening period or Washout Period (if applicable), therapy with LNG-IUS cannot be started until the subject has completed the Treatment Period and the PTFU Month 1 visit.
    - Systemic corticosteroids for > 14 days within 3 months prior to Screening or is likely to require use of systemic corticosteroids for > 7 days yearly during study participation.
        - Over-the-counter and prescription topical, inhaled, intranasal, or intra-articular injectable (for occasional use) corticosteroids are allowed.
29. Regarding other study participation, subjects must not be:
    - Currently participating in another investigational study (drug or device)
    - Participating 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.

- If a subject has participated in an investigational trial with hormonal treatment, the washout interval specified in Table 1 applies.

- Previously enrolled in either an elagolix study or a study involving another investigational oral GnRH antagonist within 3 months from last dose of study drug to Screening in Study M16-824. May not re-enroll in this study after receiving at least 1 dose of study drug.

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

Therapy[a]	Minimum Interval for Washout	Number of Menses[b] Required AFTER Completion of Washout Period (Prior to Initial Screening Visit)
Medroxyprogesterone acetate injection (Depo-Provera®; Sayana®)	10 months from injection	2 menses
GnRH antagonist and agonist (exception Synarel nasal spray and 1-month depot is 1 month) Selective progesterone receptor modulators (e.g., ulipristal acetate, vilaprisan) Danazol (Cyclomen®) Aromatase inhibitors	3 months	1 menses
Oral contraceptives[c] Oral, transdermal, or intravaginal estrogen preparations Synarel® Nasal Spray GnRH agonist – 1 month depot (e.g., Lupron Depot 3.75 mg)	1 month	
Hormonal and, sub-dermal progestin implant (e.g., Nexplanon®) NuvaRing® Progesterone-containing intrauterine system (if subject chooses to remove within 1 month of Screening)	1 month after removal	
Antifibrinolytics	2 weeks	

GnRH = gonadotropin-releasing hormone; TA MD = therapeutic area MD

a. If less than a full course of therapy is administered, the investigator should contact the AbbVie TA MD to discuss and confirm the required washout interval.

b. Subjects must complete the mandatory month of washout and subsequently have a menses. Bleeding due to withdrawal of the hormonal therapy cannot be considered the required menses.

c. Levonorgestrel 1.5 mg or ulipristal acetate 30 mg will be used for emergency contraception.

5.2 Contraception Recommendations

Subject must agree to the use of at least 2 forms of nonhormonal contraception (dual contraception) consistently throughout the Washout (if applicable), Screening, and Treatment Periods and through the end of PTFU Period. Subjects may begin taking hormonal contraception after completing the PTFU Month 1 Visit and having returned to first full menses in the PTFU Period.

Acceptable methods of dual nonhormonal contraception include:

- 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 has an LNG-IUS in place at least 6 months prior to the Screening visit and remains in place throughout the Treatment Period and PTFU Month 1 visit.
- Subject practices total abstinence from sexual intercourse, as the preferred lifestyle of the subject; periodic abstinence is not acceptable and requires dual nonhormonal contraception.
- Subject had a bilateral tubal ligation or bilateral tubal occlusion ≥ 4 months prior to Screening.
- Subject is not sexually active with men; however, periodic sexual relationship(s) with men requires the use of study-defined dual nonhormonal contraception.

5.3 Prohibited Medications and Therapy

The medications listed in Table 2 should not be taken during the Washout (if applicable), Screening, Treatment, and PTFU Periods (if applicable).

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.

If a prohibited medication is used to treat an AE or a pre-existing condition other than uterine fibroids to prevent immediate hazard during treatment period, details must be recorded in source documents and the electronic case report form (eCRF).

Table 2. Prohibited Medications

Prohibited During the Washout, Screening, Treatment, and Post-Treatment Follow-Up Periods	
GnRH agonist and antagonist, such as:	GnRH agonists: Leuprolide acetate (Lupron®), nafarelin acetate (Synarel®), goserelin acetate (Zoladex®), triptorelin (Triptodur®). GnRH antagonists (other than use of study drug as specified by protocol)
Osteoporosis medications, bisphosphonates, receptor activator of nuclear factor kappa B ligand (RANKL) inhibitors, anabolic bone agents, or recombinant human parathyroid hormone (rPTH), such as:	Denosumab, Teriparatide Fosamax®, Fosamax Plus D®, Binosto®, Boniva®, Reclast®, Zometa®, Prolia®, XGEVA®, Forteo®, Actonel®, Atelvia®, Miacalcin®, Fortical®
Glucocorticoids/corticosteroids, such as:	Systemic administration (oral, intramuscular [IM], or intravenous [IV]) (chronic use). See Section 5.4.
Prohibited During the Washout, Screening, and Treatment Periods, and Through PTFU Month 1 Visit	
Hormonal and nonhormonal estrogen supplements, such as:	Danazol (Danocrine®, Cyclomen®) Medroxyprogesterone acetate (Depo-Provera®, Provera®) Oral contraceptives Estrogen preparations Testosterone preparations Other progestins (oral, vaginal, transdermal, implantable, except emergency contraception) Human chorionic gonadotropins (hCG or hCG products) Mifepristone Selective progesterone receptor modulators (e.g., ulipristal acetate (except as emergency contraception, i.e., 30 mg) and vilaprisan) Tamoxifen Bromocriptine (Parlodel®) Cabergoline (Dostinex®) Raloxifene (Evista®, Optruma, or generics) Bazedoxifene (Conbriza) Aromatase Inhibitors (e.g., Anastrozole [Arimidex®], Exemestane [Aromasin®]) Natural estrogen preparations or herbal remedies/supplements to treat premenstrual or gynecological problems (e.g., soy-containing supplements, black cohosh)
Antifibrinolytics, such as:	Tranexamic acid (Lysteda, Cyklokapron, Cyclo-f)

Prohibited During the Washout, Screening, and Treatment Periods, and Through PTFU Month 1 Visit (Continued)	
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
Teratogens, such as:	Oral retinoids (topical applications are permitted) such as Accutane® (isotretinoin) Topiramate
Prohibited During the Screening and Treatment Periods	
Moderate or strong CYP3A inducers, such as:	**Strong Inducers:** St. John's Wort Rifampin Carbamazepine Phenytoin Mitotane Dexamethasone (chronic use) **Moderate Inducers:** Bosentan Efavirenz Etravirine Modafinil Nafcillin
Strong OATP1B1 inhibitors such as:	Cyclosporine Gemfibrozil Rifampin (single dose)

CYP3A = cytochrome P450 3A; GnRH = gonadotropin-releasing hormone; OATP = organic anion transporting polypeptide; PTFU = Post-Treatment Follow-Up

5.4 Prior and Concomitant Therapy

Any medication, procedures, or devices (e.g., intrauterine device [IUD]) used to treat uterine fibroid symptoms or HMB associated with uterine fibroids within 6 months prior to Screening (or Washout if a subject requires Washout) must be recorded in source documents and the eCRF. 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.

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), Screening Period, and during the Treatment and PTFU 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.

Information regarding potential drug interactions with elagolix can be located in the elagolix Investigator's Brochure.

Prior Hormonal/Anti-Hormonal Medications

Subjects using hormonal contraception or other hormonal/anti-hormonal therapies may be considered for study participation provided they complete the required washout. Subjects must have at least 1 menses after completion of Washout before entering into the Screening Period. Subjects entering Washout will be required to undergo study-specific procedures, as outlined in Appendix D, Study Activities.

The minimum washout intervals for hormonal medications prior to Screening are described in Table 1. If the type of hormonal product and the length of Washout Period are not listed in Table 1, a washout duration of 5 half-lives is recommended, or consult the AbbVie TA MD.

Iron Supplementation

Excessive blood loss from heavy menses may result in iron deficiency anemia. Anemia is defined by the World Health Organization (WHO) as a hemoglobin (Hgb) concentration < 12 g/dL (120 g/L) for nonpregnant women, 15 years of age and above, at sea level.[8] 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.

During Screening, all subjects with an Hgb level < 7 g/dL will be retested after receiving iron supplements; these subjects will only be eligible to randomize if their Hgb results meet eligibility prior to Day 1 (randomization) and they have not required a blood transfusion within 60 days prior to Day 1. All iron supplements taken during the study, from Screening through the Final Visit, must be recorded on the concomitant medications eCRF.

Concomitant Use of Corticosteroids and Other Medications

Chronic use (> 14 days) of systemic corticosteroids within 3 months prior to Screening through PTFU period is prohibited. Short-term use (no longer than 1 week [total of 7 days] per occurrence) of systemic glucocorticoids/corticosteroids to manage acute conditions is allowed during the Treatment Period. A maximum of 14 days over the 6-month Treatment Period is allowed during a subject's participation. Inhaled corticosteroids for the treatment of asthma are permitted. Over-the-counter and prescription topical, inhaled, intranasal, or intra-articular injectable (for occasional use) corticosteroids are allowed.

5.5 Withdrawal of Subjects and Discontinuation of Study

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 AE or noncompliance with the protocol. Subjects who withdraw from the study will not be replaced unless the investigator and AbbVie mutually agree in writing. Subjects may voluntarily withdraw or will be withdrawn from study drug treatment and/or the study at any time for reasons including, but not limited to, the following:

- 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 PTFU 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 or has a positive serum pregnancy test.
- The subject has ALT or AST elevation ≥ 5 × upper limit of normal (ULN), confirmed upon repeat testing during the Treatment Period.
- The subject develops clinically significant gynecological findings or condition that in the investigator's or AbbVie TA MD's opinion would preclude the subject from continuing in the Treatment Period due to safety reasons.
- If subject experiences a nontraumatic bone fracture during Treatment Period.
- In the investigator's opinion, the subject is unable or unwilling to comply with study-related assessments and procedures.
- Any other medical reason that AbbVie or the investigator deems appropriate.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

Treatment Interruption

AbbVie or the investigator may request that a subject temporarily discontinue study drug administration, which will be referred to as a "treatment interruption." The following are examples for reasons of treatment interruption (not all inclusive):

- AE that, based on clinical judgment, requires temporary suspension of treatment or prevents a subject from taking study drug
- Malfunction of barrier contraception or unprotected intercourse
- After a positive urine pregnancy test, while waiting for results of the serum test
- Clinical laboratory findings that require repeating or confirmation of a clinically significant value (e.g., may necessitate discontinuation from the study).
- Subject forgets to take study drug, lost study drug, etc.

If the subject has missed 10 or more consecutive days of study drug dosing, the AbbVie TA MD must be consulted to determine whether the subject may resume study drug administration or continue in the Treatment Period.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected, and the samples will be destroyed. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

Study Discontinuation

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should complete the procedures outlined for the Premature Discontinuation visit (PD visit) as soon as possible, preferably within 2 to 7 days of study drug discontinuation.

Subjects should be advised on the continued scientific importance of their PTFU data even if they discontinue treatment with study drug early. All subjects should have an onsite PTFU visit 30 days after study drug discontinuation to ensure all treatment-emergent AEs/serious adverse events (SAE) have been resolved.

All subjects who prematurely discontinue will enter the 1-month PTFU Period unless the subject decides to discontinue the study participation entirely (withdrawal of informed consent).

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug and/or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator considers necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

5.7 Study Drug

Eligible subjects will be randomly assigned to receive elagolix 150 mg QD or placebo for the 6-month double-blind Treatment Period. The treatment administration is presented in Table 3.

Table 3. Treatments Administered During the Double-Blind Treatment Period

Treatment Group	Dosing Time	Elagolix Tablet	Matching Elagolix Placebo Tablet
Elagolix 150 mg QD	AM	1	0
Placebo	AM	0	1

QD = once daily

Double-Blind Treatment Period

The study drug, consisting of elagolix 150 mg film-coated tablets, or matching placebo film-coated tablets, will be supplied in a carton with 5 blister cards. Subjects will be instructed to self-administer their study drug throughout the 6-month double-blind Treatment Period. The first dose of study drug will be administered at the site.

Identity of Investigational Product

Information about the drug formulations to be used in this study is presented in Table 4.

Table 4. Identity of Investigational Products

	Investigational Product Active	Investigational Product Placebo
Investigational product name	Elagolix 150 mg	Matching Elagolix 150 mg placebo
Active ingredient	Elagolix	None
Mode/Route of administration	Oral	Oral
Formulation	RC2	RC2
Dosage form	Film-coated tablet	Film-coated tablet
Dose and units	150 mg tablet	N/A
Frequency of administration	QD	QD
Storage conditions	15° to 25°C	15° to 25°C

N/A = not applicable; QD = once daily; RC2 = roller compaction

Compliance

During the Treatment Period visits or PD visit, the subject will be asked to confirm whether doses were taken and to provide the dates and approximate times of the last 4 scheduled doses prior to the study visit (Month 3 and Month 6). The subject-reported data will be recorded in source and in the eCRF.

5.8 Randomization/Drug Assignment

All subjects will be randomly assigned to receive either elagolix 150 mg QD or placebo centrally using an interactive response technology (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 D.

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.

Once the subject's eligibility has been confirmed 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 5.7 upon entry into the Day 1 to Month 6 Treatment Period.

Study drug must not be dispensed unless the IRT is contacted. 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.

Breaking Blind

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's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours after the blind is broken. The date and reason that the blind was broken must be recorded in the source documents and eCRF, as applicable.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

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. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

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, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE, therefore, can 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. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE 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 AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual (Appendix F), for reporting details and contact information):

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.

Serious adverse events and protocol-related nonserious AEs will be collected beginning when the subject signs the study-specific informed consent. From the time of study drug administration until PTFU Month 1 visit, all AEs, adverse events of special interest (AESIs), and SAEs will be collected whether solicited or spontaneously reported by the subject.

AbbVie will be responsible for suspected unexpected serious adverse reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with global and local requirements.

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AESIs will be monitored during the study:

- Bone fractures
- Mood and depression-related events
- Hepatic transaminase elevations

During the study, AbbVie may require additional information on AEs, SAEs, and/or AESIs to be collected and recorded in the eCRF.

Adverse Event Severity and Relationship to Study Drug

The investigator will use the following definitions to rate the severity of each AE:

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

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day of the sites being made aware of the pregnancy and study drug must be discontinued (Section 5.5). A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. If the subject has a positive serum pregnancy test during the Treatment Period, no additional study procedures will be conducted; however, an ultrasound examination will be performed (and read locally) as early as possible during the first trimester of pregnancy to assess the gestational age and document an intrauterine pregnancy.

Pregnancies identified during the Treatment Period, although not AEs, will be monitored for fetus, pregnancy, and infant outcomes. The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site's being made aware of the event. For live infant births, information on the health of the infant will be collected from the first post-delivery pediatrician visit and at 6 to 12 months after delivery.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

There will be only 1 database lock and 1 analysis after all subjects complete or prematurely discontinue from the study. The statistical methods provided in this protocol will be focused on primary efficacy analysis. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

7.2 Definition for Analysis Populations

The full analysis set (FAS) is composed of all randomized subjects who have received at least 1 dose of study drug in this study. The data from the FAS will be presented by the treatment group assigned at the time of randomization, even if a subject does not receive the correct treatment or does not follow the protocol until completion. The FAS will be used for all baseline and efficacy analyses.

The Safety Analysis Set includes all randomized subjects who received at least 1 dose of study drug. The data from the safety analysis set will be presented by the treatment actually received regardless of which treatment group was assigned at the time of randomization. If a subject takes more than 1 treatment, the subject will be analyzed in the safety analysis set as taking the treatment to which she is randomized. All safety analyses will be performed based on Safety Analysis Set.

7.3 Statistical Analyses for Efficacy

Primary Efficacy Analysis

The primary efficacy analysis will be based on the FAS, and the primary endpoint will be the proportion of responders meeting the following conditions:

- MBL volume < 80 mL at the Final Month (the last 28 days of treatment)
- ≥ 50% reduction in MBL volume from Baseline to Final Month (the last 28 days of treatment)

Subjects whose primary reason for prematurely discontinuing study drug is "lack of efficacy," or "requires surgery or invasive intervention for treatment of uterine fibroids" will be considered as non-responders.

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. For subjects who prematurely discontinue the Treatment Period prior to Month 6, the Final Month (the last 28 days prior to and including the last dose date) will be used in the primary analysis.

Additional Efficacy Analyses

Details on other efficacy analyses are provided in the SAP.

7.4 Statistical Analyses for Safety

Analysis of safety parameters will include the following:

- The number and percentage of subjects with AEs
- A summary of laboratory values

The full list of safety endpoints and corresponding analyses will be presented in the SAP.

7.5 Statistical Analyses for Pharmacokinetics/Pharmacodynamics

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

7.6 Overall Type I Error Control

No multiplicity adjustment is needed for this study as there is only 1 endpoint being analyzed and there is only 1 analysis of this endpoint.

7.7 Sample Size Determination

Approximately 48 subjects will be randomly assigned (in a 2:1 ratio) to receive either elagolix 150 mg QD (N = 32) or placebo (N = 16). The sample size will provide at least 80% power to detect a difference between the elagolix 150 mg QD group and the placebo group in the percentage of subjects meeting the primary endpoint on MBL at the Final Month of the placebo-controlled Treatment Period, with a final volume < 80 mL and an improvement of ≥ 50% from Baseline, assuming response rates of 10% for the placebo group and 55% for the elagolix 150 mg QD group with a 2-sided $\alpha = 0.05$. The above sample size was calculated using nQuery Advanced 8.1.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the ICF must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (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 investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH good clinical practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

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

12 REFERENCES

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AGC	atypical glandular cells
ALT	alanine aminotransferase
APSI	active pharmaceutical ingredient
ASC-H	atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion
ASC-US	atypical squamous cells of undetermined significance
AST	aspartate aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
BID	twice daily
BI-RADS	Breast Imaging Reporting and Data System
BMD	bone mineral density
BSO	bilateral salpingo-oophorectomy
BUN	blood urea nitrogen
CIN	cervical intraepithelial neoplasia
COVID-19	Coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
CU-IUD	copper intrauterine device
CYP3A	cytochrome P450 3A
DB	double-blind
D&C	dilation and curettage
DNA	deoxyribonucleic acid
DTP	direct-to-patient
DXA	dual x-ray absorptiometry
E2	estradiol
ECC	endocervical curettage
ECG	electrocardiogram
eCRF	electronic case report form
EC/TZ	endocervical/transformational zone
FAS	full analysis set
FDA	Food and Drug Administration

FDC	fixed-dose capsule
FSH	follicle-stimulating hormone
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV Ab	hepatitis C virus antibody
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
HIFU	high-intensity focused ultrasound
HMB	heavy menstrual bleeding
HPV	human papilloma virus
HSIL	high-grade squamous intraepithelial lesion
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IM	intramuscular
IMP	investigational medicinal product
IRB	institutional review board
IRT	interactive response technology
IU	international unit
IUD	intrauterine device
IV	intravenous
K_2EDTA	potassium ethylenediaminetetraacetic acid
LDL-C	low-density lipoprotein cholesterol
LNG-IUS	levonorgestrel intrauterine system
LSIL	low-grade squamous intraepithelial lesion
M	month
MBL	menstrual blood loss
MCH	mean corpuscular hemoglobin
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NETA	norethindrone acetate

NILM	negative intraepithelial lesion or malignancy
OATP	organic anion transporting polypeptide
Pap	Papanicolaou
PCV	Product Collection Visit
PD	premature discontinuation
PD visit	Premature Discontinuation visit
PGE1	prostaglandin E1
PGIC-MB	Patient Global Impression of Change – Menstrual Bleeding
PGIC-NBUFS	Patient Global Impression of Change - Non-Bleeding Uterine Fibroids Symptoms
PI	principal investigator
PK	pharmacokinetic
PRO	patient-reported outcome
PSQ	Physician Surgery Questionnaire
PT	post-treatment
PTFU	Post-Treatment Follow-Up
PTSD	post-traumatic stress disorder
QD	once a day
RANKL	receptor activator of nuclear factor kappa-B ligand (also known as tumor necrosis factor ligand)
RBC	red blood cells
RNA	ribonucleic acid
rPTH	recombinant human parathyroid hormone
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SIS	saline infusion sonohysterography
SOC	system organ class
SPCV	Screening Product Collection Visit
SUSAR	suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director
TAU	transabdominal ultrasound
TEAEs	treatment-emergent adverse events
TIBC	total iron binding capacity
TSH	thyroid-stimulating hormone

TVU	transvaginal ultrasound
UBQ	Uterine Bleeding Questionnaire
UFS-QoL	Uterine Fibroid Symptoms Quality of Life Questionnaire
ULN	upper limit of normal
UNSCH	Unscheduled Visit
US	United States
WBC	white blood cells
WHO	World Health Organization
WO	Washout

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-824: A Phase 4 Study to Evaluate the Safety and Efficacy of Elagolix for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

Protocol Date: 12 June 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Medical Writing
		Clinical Development
		Clinical Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology

APPENDIX D. STUDY ACTIVITIES SCHEDULE

The required study activities are shown in the following table. Individual activities are described in detail in the Operations Manual (Appendix F).

Study Activities Table (Washout, Screening, and Treatment Periods)

Activities	Washout Period (If Applicable) and Screening Period			6-Month Double-Blind (DB) Treatment Period									
	Washout (WO) Period	Screening	SPCV 1	Day 1 (Baseline)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV	Unscheduled Visit	PD Visit
INTERVIEWS & QUESTIONNAIRES													
Subject information and informed consent	✓	✓											
Eligibility criteria	✓	✓		✓									
Medical history (including tobacco and alcohol use)	✓	✓[a]		✓									
Gynecological/obstetrical history	✓	✓[a]		✓									
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-reported outcome: reason for study participation				✓									
Patient-reported outcome: C-SSRS Baseline/Screening		✓		✓									
Patient-reported outcome: C-SSRS Since Last Visit					✓	✓	✓	✓	✓	✓			✓
Patient-reported outcome: UFS-QoL				✓			✓			✓			✓
Physician Surgery Questionnaire (PSQ)				✓									
Patient-reported outcome: UBQ					✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-reported outcome: PGIC-MB					✓	✓	✓	✓	✓	✓			✓

Activities	Washout Period (If Applicable) and Screening Period			6-Month Double-Blind (DB) Treatment Period									
	Washout (WO) Period	Screening	SPCV 1	Day 1 (Baseline)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV	Unscheduled Visit	PD Visit
LABS & EXAMS													
Central Laboratory Tests: • Hematology • Chemistry • Lipid panel • Urinalysis		✓		✓			✓			✓			✓
Vitamin D		✓											
Hepatitis B/C screen		✓											
Urine test for gonorrhea and chlamydia (optional)		✓											
Endocrine: FSH and TSH with reflex		✓											
Pharmacodynamic sample: serum estradiol (E2)				✓ Pre-dose Only			✓			✓			✓
Pharmacokinetic sample (PK): elagolix plasma concentration							✓			✓			✓
Optional biomarker samples: whole blood, serum, and plasma				✓			✓			✓			✓
Urine pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓
Contraception counseling/dispense contraceptives as necessary	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Birth control attestation				✓						✓			✓
Height		✓											
Weight		✓											

Activities	Washout Period (If Applicable) and Screening Period			6-Month Double-Blind (DB) Treatment Period									
	Washout (WO) Period	Screening	SPCV 1	Day 1 (Baseline)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV	Unscheduled Visit	PD Visit
Vital Signs		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Physical exam (complete at Screening, Month 6, and PD, symptom-based at Baseline)		✓		✓						✓			✓
Gynecological (external genitalia, pelvic and breast) exam		✓								✓			✓
Pap test or colposcopy (not required if one has been done within 3 months of the Screening Visit and meets eligibility criteria)		✓											
ECG		✓											
Endometrial biopsy (not required if one has been done within 3 months of the Screening Visit and meets eligibility criteria)		✓											
Pelvic ultrasound (TAU/TVU)	✓	✓ (only if not done at WO)											
Saline infusion sonohysterography (SIS) (MRI can be performed if SIS attempt is unsuccessful or imaging is unevaluable)		✓											
Mammogram (not required if one has been done within 3 months of the Screening Visit and meets eligibility criteria)		✓											

Activities	Washout Period (If Applicable) and Screening Period			6-Month Double-Blind (DB) Treatment Period									
	Washout (WO) Period	Screening	SPCV 1	Day 1 (Baseline)	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV	Unscheduled Visit	PD Visit
Dispense sanitary products collection kit keg, collection bags, etc. for (AH) testing		✓	✓	✓	✓	✓	✓	✓	✓		✓		
Return sanitary products for AH testing		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
℞ TREATMENT													
Randomization with drug assignment				✓									
Dispense study drug				✓	✓	✓	✓	✓	✓				
Drug accountability					✓	✓	✓	✓	✓	✓			✓

C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle-stimulating hormone; MRI = magnetic resonance imaging; PD = premature discontinuation; PGIC-MB = Patient Global Impression of Change – Menstrual Bleeding; PK = pharmacokinetic; PSQ = Physician Surgery Questionnaire; SIS = Saline infusion sonohysterography; TAU = transabdominal ultrasound; TSH = thyroid-stimulating hormone; TVU = transvaginal ultrasound; UBQ = Uterine Bleeding Questionnaire; UFS-QoL = Uterine Fibroid Symptoms Quality of Life Questionnaire; WO = Washout

a. Only if not performed during Washout.

Study Activities Table (Post-Treatment Follow-Up Period)

Activities	1 -Month Post-Treatment Follow-Up (PTFU) Period		
	Month 1	Unscheduled Visit	PD Visit
On-site visit	✓	✓	✓
INTERVIEWS & QUESTIONNAIRES			
Adverse event assessment (see Section 6.1)	✓	✓	✓
Prior/Concomitant Therapy	✓	✓	✓
LABS & EXAMS			
Pharmacodynamic sample: serum estradiol (E2)	✓		
Central laboratory tests: • Liver function tests • Lipids	✓		
Urine pregnancy test	✓		
Contraception counseling/dispense contraceptives as necessary	✓		
Vital signs	✓		

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	27 November 2018
Version 2.0	28 August 2019
Version 3.0	17 October 2019
Administrative Change 1	11 May 2020

The purpose of this version is to truncate assessments in a clinically appropriate manner, as this will now become an exploratory study to evaluate the effectiveness of the 150 mg elagolix alone dose to reduce HMB associated with uterine fibroids. Other administrative revisions and minor clerical errors were corrected for consistency throughout the protocol in addition to the following:

- Removal of dual x-ray absorptiometry (DXA) scan from all timepoints in the study. Monitoring of BMD in the study will not be included as part of protocol-specified procedures.

  Rationale: This study evaluates the low dose regimen of 150 mg QD for uterine fibroids administered for 6 months. There is sufficient safety data for BMD at the 150 mg QD dose.

- Removal of the Day 1 and Month 6 pelvic ultrasound (TAU and TVU).

  Rationale: Pelvic ultrasound will only be used to determine eligibility. Fibroid and uterine volume are no longer endpoints in the study.

- The PTFU Period was shortened from 12 months to 1 month.

  Rationale: An extended PTFU period is no longer necessary due to removal of DXA/BMD assessment.

- Removal of secondary endpoints in the study

  Rationale: Study changed to exploratory study.

- Reduction of sample size from 150 to 48

  Rationale: Study changed to exploratory study.

- Additional directions for protocol modifications related to the Coronavirus disease 2019 (COVID-19) pandemic were added to Operations Manual Section 2.2, Section 3.7, Section 3.8, Section 3.11, Section 3.22, Section 3.24, and Section 6.1.

  Rationale: **T**o describe alternative processes that may be needed because of the COVID-19 pandemic.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M16-824

Safety and Efficacy of Elagolix for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Elagolix (ABT-620)

FULL TITLE: A Phase 4 Study to Evaluate the Safety and Efficacy of Elagolix for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women

1 CONTACTS

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Biomarker Sample Lab	Genomic Technologies, Genomics Resource Center (GRC) [redacted] AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Phone: Email: [redacted]

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2 PROTOCOL ACTIVITIES BY VISIT

2.1 Individual Washout/Screening Period Visit Activities

This section presents a list of activities performed during the Washout/Screening Period, organized by visit. The dot pattern depicted at the beginning indicates the place of the visit in the overall Washout/Screening Period Activity Schedule. There are 3 dots representing the 3 visit types that are associated with the Washout/Screening Period (Washout, Screening, and Product Collection Visit [PCV]).

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

WASHOUT:

INTERVIEW	• Subject information and informed consent • Eligibility criteria • Medical history (including tobacco and alcohol use)	• Gynecological/obstetrical history • Adverse event (AE) assessment • Prior/concomitant therapy
EXAM	• Contraception counseling/dispense contraceptives as necessary	• Pelvic ultrasound (transabdominal ultrasound [TAU]/transvaginal ultrasound [TVU])
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	

SCREENING:

INTERVIEW	• Subject information and informed consent • Eligibility criteria • Medical history (including tobacco and alcohol use; only if not performed during Washout)	• Gynecological/obstetrical history (only if not performed during Washout) • AE assessment • Prior/concomitant therapy
PRO	• Columbia-Suicide Severity Rating Scale (C-SSRS) Screening	

EXAM	• Contraception counseling/dispense contraceptives as necessary • Height • Weight • Vital signs • Complete physical examination • Gynecological (external genitalia, pelvic and breast) exam • Pap test • Electrocardiogram (ECG) • Endometrial biopsy • Pelvic ultrasound (TAU/TVU) (only if not performed during Washout)	• Saline infusion sonohysterography (SIS) • Magnetic resonance imaging (MRI) if SIS cannot be obtained or is unevaluable • Mammogram • Dispense sanitary products collection kit (keg, collection bag, etc.) • Begin collection of sanitary products
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	
CENTRAL LAB	• Central laboratory tests (hematology, chemistry, lipid panels, urinalysis) • Vitamin D • Hepatitis B/C screen	• Urine test for gonorrhea and chlamydia (optional) • Endocrine follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) with reflex

NOTES: Final reports for Pap tests or colposcopy, endometrial biopsy and/or mammogram (only for subjects who will be 40 years of age or older at the time of consent) conducted outside of the study within the prior 3 months, must be obtained for the subject's Screening Visit or within 2 weeks of completing the Screening Visit if they are to be used for eligibility. If the reports cannot be obtained, the subject will have to undergo these study procedures during the specified Screening Period to assess for eligibility into the study.

Results are to be reviewed by the principal investigator and deemed to meet eligibility requirements.

Screening-related procedures to assess for eligibility must be conducted within first 1.5- to 2.5-month duration. However, in the event the cycle or product collection is not complete within 2.5 months during the Screening Period, the Screening Period may be extended with prior Therapeutic Area Medical Director (TA MD) approval and would result in a longer duration of participation for the subject than outlined.

It is recommended that TVU/TAU to determine whether subject has qualifying fibroids be done early in Screening prior to Screening PCV1.

SCREENING PRODUCT COLLECTION VISIT (SPCV):

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) • Return sanitary products
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood samples

Note: Sanitary product collection should be stopped as soon as it is determined that there are "no qualifying fibroids" per central reader and the collected sanitary product should not be submitted to KCAS for alkaline hematin estimation. Any sanitary product collected by the subject should be discarded on site.

2.2 Individual Treatment Period Visit Activities

This section presents a list of activities performed during the Treatment Period, organized by visit. The dot pattern depicted at the beginning indicates the place of the visit in the overall Treatment Period Activity Schedule. There are 10 dots representing the 10 visit types that are associated with the treatment Period beginning with Day 1 (Baseline), Month 1 to 6, Premature Discontinuation (PD), Product Collection Visit, and Unscheduled Visit (UNSCH).

Scheduled monthly visits during the Treatment Period are based on a 28-day month. Month 1 through 5 visits must occur within ± 5 days of the projected date. A -5 or +6 days 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.

In the event that a subject or study personnel cannot come to the site because of the COVID-19 pandemic, study visits may be conducted over the phone where feasible, and AbbVie should be notified.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

Day 1 (BASELINE):

INTERVIEW	• Eligibility criteria • Medical history (including tobacco and alcohol use) • Symptom-directed gynecological/obstetrical history	• AE assessment • Prior/concomitant therapy • Physician Surgery Questionnaire (PSQ)
EXAM	• Contraception counseling/dispense contraceptives as necessary • Birth control attestation • Vital signs	• Symptom-directed physical exam • Dispense sanitary products collection kit (keg, collection bag, etc.) • Return sanitary products
PRO	• Reason for Study Participation Questionnaire • C-SSRS Baseline/Screening	• Uterine Fibroid Symptoms Quality of Life (UFS-QoL)
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (if a keg is returned)
CENTRAL LAB	• Central laboratory tests (hematology, chemistry, lipid panels, urinalysis) • Pharmacodynamic sample (serum estradiol) (predose only)	• Optional biomarker sample: whole blood (deoxyribonucleic acid [DNA]/ribonucleic acid [RNA]/serum/plasma)
TREATMENT	• Randomization/drug assignment	• Dispense study drug (the first dose should be administered at the site)

NOTES: The Baseline visit should occur on Days 1 through 10 of the start of menses (defined as the first day of menstrual flow).

If urine pregnancy test is positive study drug must not be dispensed

If urine pregnancy test is positive and confirmed by a positive serum pregnancy test, subject should be screen failed.

MONTH 1:

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) and remind subject to continue collection of sanitary products • Return sanitary products
PRO	• C-SSRS Since Last Visit • Uterine Bleeding Questionnaire (UBQ) (if no sanitary product is returned)	• Patient Global Impression of Change – Menstrual Bleeding (PGIC-MB)
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (if a keg is returned)
TREATMENT	• Dispense study drug	• Drug accountability

NOTES: One month = 28 days.

MONTH 2:

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) and remind subject to continue collection of sanitary products • Return sanitary products
PRO	• C-SSRS Since Last Visit • UBQ (if no sanitary product is returned)	• PGIC-MB
LAB	• Urine pregnancy test	• Draw venous blood sample (if a keg is returned)
TREATMENT	• Dispense study drug	• Drug accountability

NOTES: One month = 28 days.

MONTH 3:

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) and remind subject to continue collection of sanitary products • Return sanitary products
PRO	• C-SSRS Since Last Visit • UFS-QoL	• UBQ (if no sanitary product is returned) • PGIC-MB
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (if a keg is returned)
CENTRAL LAB	• Central laboratory tests (hematology, chemistry, lipid panels, urinalysis) • Pharmacodynamic sample (serum estradiol)	• Pharmacokinetic sample: Elagolix plasma concentration • Optional biomarker sample: whole blood (DNA/RNA/serum/plasma)
TREATMENT	• Dispense study drug	• Drug accountability

NOTES: One month = 28 days.

MONTH 4:

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) and remind subject to continue collection of sanitary products • Return sanitary products
PRO	• C-SSRS Since Last Visit • UBQ (if no sanitary product is returned)	• PGIC-MB
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (if a keg is returned)
TREATMENT	• Dispense study drug	• Drug accountability

NOTES: One month = 28 days.

MONTH 5:

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) and remind subject to continue collection of sanitary products • Return sanitary products
PRO	• C-SSRS Since Last Visit • UBQ (if no sanitary product is returned)	• PGIC-MB
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (if a keg is returned)
TREATMENT	• Dispense study drug	• Drug accountability

NOTES: One month = 28 days.

MONTH 6:

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Birth control attestation • Vital signs • Complete physical examination	• Gynecological (external genitalia, pelvic and breast) exam • Return sanitary products
PRO	• C-SSRS Since Last Visit • UFS-QoL	• UBQ (if no sanitary product is returned) • PGIC-MB
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (if a keg is returned)
CENTRAL LAB	• Central laboratory tests (hematology, chemistry, lipid panels, urinalysis) • Pharmacodynamic sample (serum estradiol)	• Pharmacokinetic sample: Elagolix plasma concentration • Optional biomarker sample: whole blood (DNA/RNA/serum/plasma)
TREATMENT	• Drug accountability	

NOTES: One month = 28 days.
A -5 or +6 days 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.

PRODUCT COLLECTION VISIT (Occurring Between Day 1 and Month 6):

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Vital signs	• Dispense sanitary products collection kit (keg, collection bag, etc.) and remind subject to continue collection of sanitary products • Return sanitary products
PRO	• UBQ (if no sanitary product is returned)	
LAB	• Draw venous blood sample (if a keg is returned)	

NOTES: If timing of PCV aligns with a monthly visit, the keg will be collected during that monthly visit, and a separate PCV visit is not required for that month.

UNSCHEDULED VISIT (UNSCH):

INTERVIEW	• Adverse event assessment • Prior/concomitant therapy
PRO	• UBQ (if no sanitary product is returned)
LAB	• Draw venous blood sample (if a keg is returned)

NOTES: In the event an unscheduled visit is necessary during the Treatment Period, the site will perform at minimum, 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.

PREMATURE DISCONTINUATION (PD) VISIT:	○ ○ ○ ○ ○ ○ ○ ○ ○ ●	
INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling/dispense contraceptives as necessary • Birth control attestation • Vital signs • Complete physical examination	• Gynecological (external genitalia, pelvic and breast) exam • Return sanitary products (only for subjects with a PD visit prior to Month 6)
PRO	• C-SSRS Since Last Visit • UFS-QoL	• UBQ (if no sanitary product is returned) • PGIC-MB
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	• Draw venous blood sample (only if PD prior to Month 6 and a keg is returned)
CENTRAL LAB	• Central laboratory tests (hematology, chemistry, lipid panels, urinalysis) • Pharmacodynamic sample (serum estradiol)	• Pharmacokinetic sample: Elagolix plasma concentration • Optional biomarker sample: whole blood (DNA/RNA/serum/plasma)
TREATMENT	• Drug accountability	

NOTES: All subjects must enter Post-Treatment Follow-Up (PTFU) Period unless subject withdraws consent or becomes pregnant during the Treatment Period.

2.3 Post-Treatment Follow-Up Visit Activities

This section presents a list of activities performed at the PTFU Month 1 visit.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

POST-TREATMENT
FOLLOW-UP MONTH 1
(30 Days Post last day of study drug) (On-Site): ● ○ ○ ○ ○ ○ ○

INTERVIEW	• AE assessment • Prior/concomitant therapy	
EXAM	• Contraception counseling • Vital signs	
LAB	• Urine pregnancy test (if positive, perform a serum pregnancy test)	
CENTRAL LAB	• Pharmacodynamic sample (serum estradiol)	• Liver function tests • Lipid panel

UNSCHEDULED VISIT (UNSCH) (On-Site): ○ ○ ○ ○ ○ ● ○

INTERVIEW	• AE assessment • Prior/concomitant therapy

NOTES: In the event an Unscheduled Visit is necessary during the Post-Treatment Follow-up Period, the site will perform at minimum, 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. 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.

PD VISIT (Site Visit): ○ ○ ○ ○ ○ ○ ●

INTERVIEW	• AE assessment • Prior/concomitant therapy

3 STUDY PROCEDURES

3.1 Subject Information and Informed 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 or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other

signatories according to local requirements. A copy of the signed informed consent 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.

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the exploratory research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study.

Information regarding benefits 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.

3.2 Eligibility Criteria

Each investigator will employ their clinical judgment in conjunction with protocol-specified eligibility criteria to determine if a subject is eligible for the study. If further clarification is required, questions should be directed to the AbbVie Therapeutic Area Medical Director (TA MD) listed in Section 1.

3.3 Medical History

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

3.4 Gynecological/Obstetrical and Uterine Fibroid History

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

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

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

The gynecological/obstetrical and uterine fibroid history will be reviewed and should be updated if needed prior to dosing on Day 1 (randomization) and will serve as the Baseline for clinical assessment.

3.5 Adverse Event Assessment

Please refer to Section 6 of the study protocol.

3.6 Prior and Concomitant Therapy

Prior and concomitant medications will be assessed at the time points specified in Section 2 and as described in the protocol.

3.7 Patient-Reported Outcomes and Rating Scales

Prior to the start of the study, AbbVie and/or its designee will provide detailed instructions and training for study site staff administering these scales. The objective of this training is to establish uniformity across sites in administration of these rating instruments. The subjects and/or the investigator or site staff will complete the following questionnaires as appropriate at the time points indicated in Section 2; the questionnaires should be administered before any other study procedures are performed at that visit. Subjects and site staff will be asked to record their responses electronically (which will then be entered into the electronic case report form (eCRF), as applicable).

In the event that a subject or study personnel cannot come to the site because of the COVID-19 pandemic, patient-reported outcome entries may be administered by site staff over the phone and responses collected on paper (source) and transcribed into EDC or entered by site staff directly into an electronic system. AbbVie should be notified.

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

The UFS-QoL[1] is a disease-specific self-administered questionnaire used to measure health-related quality of life in women with symptomatic uterine fibroids. At the times specified in Section 2, each

subject will be asked to complete a modified (4-week recall) UFS-QoL Questionnaire to report fibroid-related symptoms experienced during the previous 4 weeks.

Reason for Study Participation Questionnaire

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

Physician Surgery Questionnaire (PSQ)

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

Uterine Bleeding Questionnaire (UBQ)

Subjects who did not return a sanitary product collection keg (for alkaline hematin menstrual blood loss analysis) at applicable on-site visits (scheduled on-site visit, Product Collection Visit, Unscheduled, or the PD visit) during the study 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 why they did not return sanitary product collection keg at the on-site visit. This response will be recorded on the UBQ by the site staff. Subjects who did not return the keg will be retrained on product collection.

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

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

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS[2] 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 and to 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. Site staff will administer the Screening/Baseline C-SSRS questionnaire in Screening and on Day 1. During the Treatment Period, site staff will administer the C-SSRS Since Last Visit questionnaire at the time points specified in Section 2.2. The C-SSRS administered at the Day 1 Visit will serve as the Baseline for clinical assessment.

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. In addition, any subject noted to have history of any suicide attempts "ever" on C-SSRS or via clinical interview, is not eligible for randomization. If the subject expresses suicidal ideation or suicidal behavior on the C-SSRS or via clinical interview at any time during the study, the investigator should take appropriate action to protect the subject (including possible discontinuation from the study and referral for appropriate psychiatric care) and then notify the AbbVie TA MD.

3.8 Clinical Laboratory Tests

Laboratory samples will be assessed using a certified central laboratory selected for this study. 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 12-lead ECG recording are conducted at a visit.

In the event that the central laboratory cannot be used to test samples because of the COVID-19 pandemic, samples may be obtained at a local laboratory or by a home health care service. AbbVie should be notified.

All clinical laboratory samples will be shipped to the central laboratory, with the exception of the venous blood sample for alkaline hematin analysis, which will be sent to the alkaline hematin laboratory.

All screening laboratory results must be reviewed prior to randomization, including any repeated test results. Screening laboratory tests may be repeated one time prior to Day 1; however, results must satisfy entry criteria prior to randomization. Subjects will not be randomized on Day 1 if screening laboratory results do not meet entry criteria or are assessed as clinically significant by the investigator. The laboratory test results obtained prior to Day 1 will serve as the Baseline for clinical assessment.

The central laboratory will provide the laboratory results to the investigative site where they will be reviewed, signed, and dated by the investigator. The investigator will receive sponsor-defined alerts from the central laboratory. For any value outside of the reference range and/or sponsor-defined alerts, the investigator will review and indicate on the report if the result is clinically significant or not clinically significant. The investigator will evaluate clinically significant laboratory values per standard of care, which may include repeating the test to verify the out-of-range value. Clinically significant laboratory abnormalities after randomization may be documented as AEs if they require discontinuation or at the discretion of the investigator (see protocol).

Samples will be obtained for the laboratory tests listed in Table 1 at the time points specified in Section 2.

Table 1. Clinical Laboratory Tests

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry
(After Minimum 8-Hour Fast)</th><th>Lipid Panel
(After Minimum 8-Hour Fast)</th></tr>
<tr><td rowspan="2">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)</td><td rowspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Serum creatinine
Glucose
Calcium
Total protein
Albumin
Total bilirubin
Alanine aminotransferase
Aspartate aminotransferase
Alkaline phosphatase
Screening only
Serum iron
Serum ferritin
Total iron binding capacity (TIBC)
Vitamin D</td><td>Low-density lipoprotein cholesterol (LDL-C)
High-density lipoprotein cholesterol (HDL-C)
Triglycerides
Total cholesterol</td></tr>
<tr><td>Endocrine Panel (Screening Only)
Follicle-stimulating hormone (FSH)
Reflexive thyroid-stimulating hormone (TSH)</td></tr>
<tr><td>Urinalysis</td><td>Pregnancy Test</td><td>Other Tests (Screening Only)</td></tr>
<tr><td>Specific gravity
Ketones
Protein
Blood
Glucose
pH</td><td>Serum pregnancy (only when urine pregnancy test is positive)</td><td>Hepatitis B surface antigen (HBsAg)
Hepatitis C virus antibody (HCV Ab)</td></tr>
</table>

Clinical Chemistry/Lipid Panel

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 the sample is obtained later in the day and/or not under fasting conditions. If the sample was obtained with less than 8 hours of fasting, the source documents and the lab requisition should be marked to indicate that the sample was obtained under nonfasting conditions.

Pregnancy Tests (Serum and Urine)

Urine pregnancy tests will be performed at the time points specified in Section 2, in all subjects regardless of sexual activity status or method of contraception, including subjects who are surgically sterilized.

The urine pregnancy test result on Day 1 must be reviewed and confirmed to be negative prior to randomization.

During treatment period, a positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. Study drug must not be dispensed if the subject has a positive urine pregnancy test result at any visit during the Treatment Periods (including Day 1 result). The site will immediately inform the subject to discontinue study drug temporarily while the subject waits for the results of the serum pregnancy test. If a serum pregnancy test result is positive, the subject will be prematurely discontinued from the study drug. The site should instruct the subject to complete a Premature Discontinuation visit within 2 to 7 days of study drug discontinuation.

In the event that a subject or study personnel cannot come to the site for a study visit requiring a urine pregnancy test because of the COVID-19 pandemic, home pregnancy test kits may be provided to subjects to self-administer at home and report results to study site over the phone.

If the subject becomes pregnant at any time after randomization up through 30 days after the last dose of study drug, an ultrasound examination will be performed as early as possible during the first trimester of pregnancy to assess the gestational age and estimated date of delivery. Refer to Section 4.4 for instructions on reporting of a pregnancy to the sponsor and the required follow-up on the subject's fetus, pregnancy, and infant outcomes.

Urine Test for Gonorrhea and Chlamydia (Optional)

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

3.9 Pharmacokinetic and Pharmacodynamic Sampling

Blood samples for assay of elagolix, also known as pharmacokinetic samples, will be collected by venipuncture into 3-mL evacuated K_2-ethylenediaminetetraacetic acid (K_2EDTA)-containing collection tubes at the time points specified in Section 2. Samples will be collected regardless of the time of last dose. Sufficient blood will be collected to provide approximately 1 mL of plasma from each sample.

Blood samples for assay of estradiol, also known as pharmacodynamic samples, will be collected by venipuncture into 4-mL evacuated collection tubes without anticoagulant (red cap, no gel separators to be used) at the time points specified in Section 2. On Day 1, estradiol samples will be collected prior to dosing. Samples collected at all visits other than Day 1 will be drawn at any time during the visit. Sufficient blood volume will be collected to provide approximately 1.6 mL of serum from each sample.

The date and time of blood collections will be recorded on the Central Laboratory Requisition Form (see Section 5.7 of the protocol under compliance for recording the times of the last 4 doses prior to study visit).

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

The Bioanalysis Department at AbbVie will use validated assays to determine plasma concentrations of elagolix and serum concentrations of estradiol.

3.10 Biomarker Research Sampling

Optional biospecimens (whole blood, serum, and plasma) for biomarker research will be collected at the time points specified in Section 2. All biomarker samples should be collected, labeled, and shipped as outlined in the study-specific lab manual.

AbbVie (or people or companies working with AbbVie) will store the biomarker samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on elagolix (or drugs of this class) or uterine fibroids and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.11 Contraception Counseling/Dispense Contraceptives

The sponsor will train investigators and study staff on the importance of contraception in this clinical trial. The investigator or designated study staff will counsel subjects (excluding those who have had a bilateral tubal ligation or bilateral tubal occlusion) at every on-site visit throughout study participation on the importance of pregnancy prevention and the use of appropriate and effective methods of contraception.

Subjects must agree to use at least 2 forms of nonhormonal contraception (dual contraception) as indicated in the protocol. If a subject has used LNG-IUS at least 6 months prior to the Screening visit and that remains in place throughout the Treatment Period through the PTFU Month 1 visit, she is not required to use 2 forms of nonhormonal contraception.

In the event that a subject or study personnel cannot come to the site for dispensing of nonhormonal contraceptive supplies because of the COVID-19 pandemic, nonhormonal contraceptive supplies may be provided to subjects via alternative means.

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

1. The informed consent form will include an attestation requiring the subject to confirm in writing (via signature) her full awareness that the potential risks of study drug on the unborn child are unknown, and therefore, she must not get pregnant during the entire time of study participation, and that she agrees to consistently use protocol-required nonhormonal contraception throughout her study participation.
2. The investigator or designated study staff will counsel the subject that the study drug is not contraceptive, that ovulation may occur even though the study drug may have altered menstrual cycle patterns, and that fetal abnormalities have been reported in women who have received elagolix in clinical studies; however, it is unknown whether these abnormalities were the result of taking elagolix.

3. The sponsor will provide training materials to the sites for instructing subjects on the types of protocol-allowed contraception methods, their effectiveness, and proper use.
    - The sponsor will provide all investigative sites with a supply of materials to promote pregnancy prevention, including contraceptives (e.g., condoms and spermicides) to provide to subjects at no charge.
    - Subjects should only use the pregnancy prevention materials provided by the sponsor as these products have undergone analytical testing by the analytical lab to confirm there is no or limited interference with the alkaline hematin method.
    - Subjects will be allowed to choose an acceptable contraception method of their choice from the contraceptives provided by the sponsor and will be expected to consistently practice the allowable methods of contraception. The site will assess the subject's basic understanding of the proper contraceptive use through discussion and demonstration of proper techniques, if needed, including proper diaphragm use.
    - The site will provide contraceptives and other supplies (e.g., lubricants) to subjects at the time points specified in Section 2, as necessary.
    - The source documents will capture the date that initial contraception counseling was performed, whether the subject meets protocol criteria for not requiring use of dual contraception, and the type of contraceptive provided to the subject (as applicable). At subsequent study visits, the source documents will capture any change in contraceptive method, use of a non-study supply brand, and whether additional contraceptives were provided to the subject.
    - The subject will be asked to attest by signature at the time of consent, and subsequently in a stand-alone attestation form at all on-site study visits that allowable methods of contraception, as described during the pregnancy prevention counseling, are being practiced.
    - For subjects who have had a bilateral tubal ligation or bilateral tubal occlusion, (including Essure®) or LNG-IUS, attestation is only required to be collected once during the study prior to randomization, ideally at the time of consent. Additionally, these subjects do not require contraception counseling at any study visit or the associated documentation of that counseling.
4. Monthly study contacts are used to promote frequent interaction with site staff and opportunities for continued education.
5. At each Treatment Period visit (on-site), the proper use of contraception will be reinforced to address possible ineffective use and the risk of unexpected pregnancy due to unprotected sexual activity.

3.12 Height and Weight

Height and body weight will be measured at Screening (Section 2.1). The subject will wear lightweight clothing and no shoes during weighing. The weight measurement at Screening will serve as the Baseline for clinical assessment.

3.13 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at the time points specified in Section 2. The blood pressure and heart rate measurements should be taken prior to scheduled blood collections (if applicable). Subjects should be seated for a minimum of 5 minutes before vital signs are taken; subjects are to remain seated when vital signs are taken. Measurements should be assessed consistently throughout the study and will be recorded in the source documents and eCRF.

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

3.14 Physical Examination

A complete physical examination will be performed at the time points specified in Section 2. The complete physical examination performed during Screening will serve as the Baseline for clinical assessment. A brief, symptom-directed physical examination will be performed at the Day 1 visit.

Any significant physical examination findings after the first dose will be recorded as AE. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

3.15 Gynecological (Pelvic and Breast) Examination

A complete breast and pelvic examination, including external genitalia, will be performed at the time points specified in Section 2. The complete breast and pelvic examination completed during Screening will serve as the Baseline for clinical assessment.

3.16 Pap Test

A Pap test will be performed in Subjects > 21 years of age during the Screening Period unless the Subject has had a Pap smear or colposcopy within 3 months of the start of Screening, and results are reviewed by the principal investigator and deemed to meet eligibility requirements as outlined in Figure 1, Pap Test Eligibility. For those subjects who require a Pap smear during the Screening Period, the Pap test will be performed using the Thin Prep® Pap Test™ provided and analyzed by the central laboratory. If the subject is experiencing uterine bleeding that precludes the performance of the Pap test, this procedure should be performed as soon as possible after the uterine bleeding has ended. In the case of an unsatisfactory sample, the Pap test can be repeated. The repeat Pap test should also be performed when the subject is not experiencing uterine bleeding. In order to be enrolled in the study, the Pap test must meet eligibility requirements as outlined in Figure 1, Pap Test Eligibility.

Subjects who are 25 to 51 years of age, with the Pap diagnosis of atypical squamous cells of undetermined significance (ASC-US), or low grade squamous intraepithelial lesion (LSIL) and those > 30 years of age with negative intraepithelial lesion or malignancy (NILM) but absent or insufficient

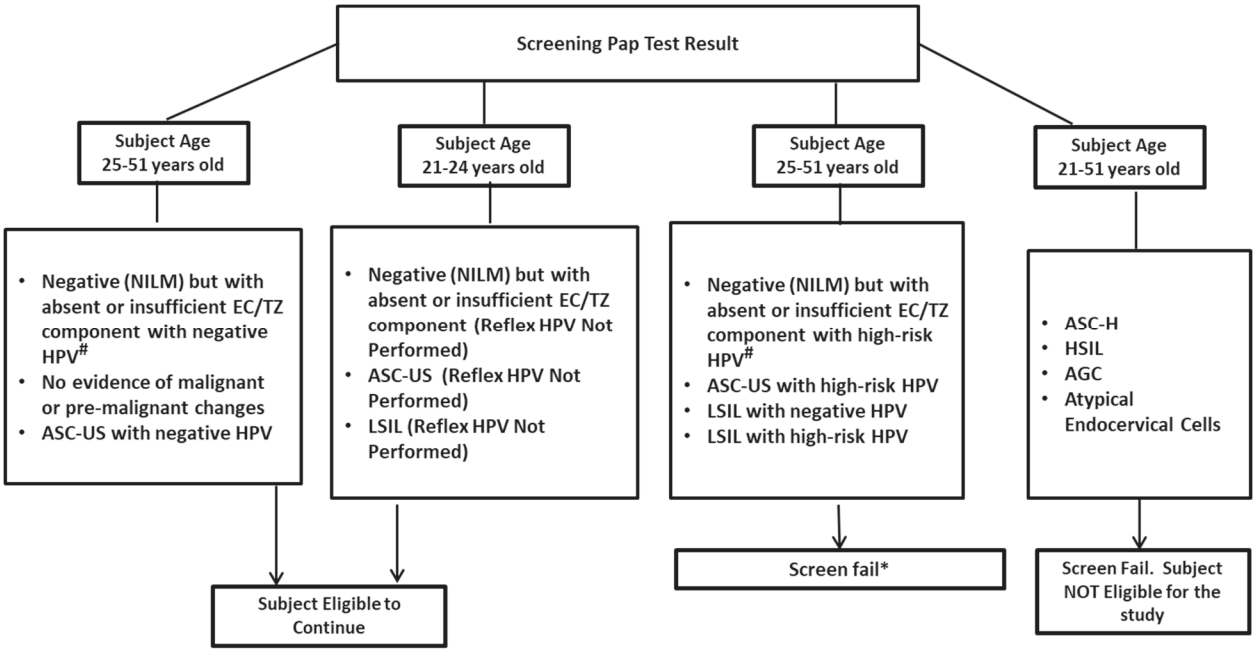
endocervical/transformational zone (EC/TZ) component will have reflex human papillomavirus (HPV) testing as outlined in Figure 1. Those with high-risk HPV, NILM with absent or insufficient EC/TZ, or LSIL with or without high-risk HPV will be screen failed and may undergo additional evaluation/colposcopy outside of the protocol per local guidelines or standard of care.

If a Subject has a colposcopy performed outside of the study, they may be rescreened if they have no other exclusionary criteria and has had an adequate colposcopy with a negative endocervical sample post colposcopy. If biopsies are performed, they must show a histological diagnosis of cervical intraepithelial neoplasia (CIN) 1 or less with an adequate colposcopy and a negative endocervical sample post colposcopy.

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

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

Figure 1. Pap Test Eligibility



AGC = atypical glandular cells; ASC-H = atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; EC/TZ = endocervical/transformational zone; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NILM = negative intraepithelial lesion or malignancy

* If a colposcopy is performed outside the study, subject may be eligible to rescreen provided the colposcopy results show a histologically negative endocervical curettage (ECC), and if biopsies were performed, they must be CIN 1 or less.

\# Reflex performed only if subject is > 30 years of age.

3.17 Endometrial Biopsy

An endometrial biopsy will be performed in all subjects during the Screening Period unless final report of endometrial biopsy done within 3 months of Screening are available and results are reviewed by the principal investigator and deemed to meet eligibility requirements. Subjects must have a negative urine pregnancy test within 24 hours before undergoing the 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 laboratory or any other endometrial biopsy instruments available at the study site.

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

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, including SIS.

The investigator must obtain and review biopsy results from the central laboratory to ensure that eligibility criteria are met before the subject can be randomized on Day 1. In case of an insufficient sample, the biopsy may be repeated; however, results must be available prior to randomization. If there is a need for an office hysteroscopy to obtain the endometrial biopsy sample, the AbbVie TA MD (Section 1) should be consulted. If biopsy needs to be repeated and SIS is pending or repeat SIS is requested by central reader, it is recommended that both procedures be planned together; the endometrial biopsy should be performed immediately after SIS. Subjects must have an adequate endometrial biopsy, (i.e., results show no endometrial pathology) to be eligible for randomization.

If an abnormal finding such as endometritis, hyperplasia (with or without atypia), or endometrial cancer is reported, subjects will not be eligible for randomization into the study. If the investigator determines that an abnormal finding can be treated outside of the protocol, the subject will be considered a screen failure, but may be rescreened after treatment per rescreening guidelines in the protocol.

3.18 12-Lead Electrocardiogram

12-lead ECG will be performed at the designated study visits as specified in Section 2.1. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

3.19 Mammogram

A mammogram will be obtained during Screening (only for subjects who will be 40 years of age or older at the time of consent) unless the subject had a mammogram performed within 3 months prior to Screening and results are reviewed by the principal investigator and deemed to meet eligibility requirements. Local mammogram results and final interpretation must be entered into the eCRF upon receipt.

A local radiologist will read mammograms and that radiologist's interpretation will be used to determine if a subject meets eligibility criteria.

- Subjects with normal or benign findings or Breast Imaging Reporting and Data System (BI-RADS) Classifications 1, 2, or 3 (via mammogram or other mode of imaging) will be eligible for the study.
- Subjects with an abnormal mammogram or BI-RADS 4, 5, or 6 will not be eligible for 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 the study. Any further imaging or testing will be performed outside of the protocol and should follow standard of care.
- If a subject's mammogram results are incomplete ([BI-RADS] 0) and need to be repeated, the AbbVie TA MD does not need to be contacted for approval before the repeat mammogram or other mode of imaging (e.g., ultrasound, spot compression) is conducted. If results meet entry requirements, the subject will be allowed to continue in Screening.

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

3.20 Central Imaging Procedures

Pelvic Ultrasound: TAU and TVU

The pelvic ultrasound (TAU, TVU, SIS) will be performed by the investigative sites' or affiliated radiology department. If magnetic resonance imaging (MRI) is requested by central reader for further evaluation of endometrial cavity it will be performed by the investigative sites' or affiliated radiology department. The ultrasonographer at each investigative site will be required to acquire the ultrasound, SIS, and MRI (if applicable) images according to the Imaging Acquisition Guidelines provided by the central reader. Images (still images and video clips as requested) should be transmitted to the central reader to determine eligibility for entry into the study.

The principal investigator should review the pelvic ultrasound images or report to assess eligibility. If no eligible fibroids are found on local read, the subject should be screen-failed, and no images should be

submitted to central reader for further assessment. To maintain screening timelines, it is recommended that there be short turnaround time for local read.

The investigator or designee is responsible for review of local ultrasound, SIS reports, and/or MRI images for subject safety. Any abnormal findings that are clinically significant and that requires medical intervention should be reported as AE. 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.

Central Reader 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
- Volume of largest fibroid at Baseline in cubic centimeters
- Uterine volume in cubic centimeters
- Presence of ovarian cysts: Number; size (cm); location (right/left ovary); simple/complex/corpus luteum
- 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 eligibility criteria based on the presence of focal intracavitary lesions including:

- Large endometrial polyp (≥ 1 cm)
- Intracavitary submucosal pedunculated fibroid (FIGO Type 0)

Subjects should have a negative urine pregnancy test within 24 hours before undergoing the SIS. It is recommended that video clips be captured during SIS (see Imaging Acquisition Guidelines).

The SIS should be performed as early as possible during the Screening Period to rule out any exclusionary findings. For subjects entering Washout, a SIS will not be performed until the subject enters the Screening Period to limit the number of invasive procedures before her eligibility is fully determined.

If a subject has an endometrial polyp ≥ 1 cm and desires to have the polyp removed outside of the study (before 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/or uterine volume as assessed by central reader but do not have SIS images that adequately characterize the endometrial cavity, SIS may be repeated. Alternatively, an MRI may be performed in lieu of SIS if SIS cannot be performed (e.g., due to location or

size of fibroids) or images are unevaluable. The AbbVie TA MD should be consulted if the investigator plans to perform MRI.

If SIS needs to be repeated and endometrial biopsy is pending or repeat endometrial biopsy is needed, it is recommended that both procedures be planned together; the endometrial biopsy be performed immediately after SIS.

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).

3.21 Collection of Sanitary Products

Quantitative measurement of the volume of menstrual blood loss (MBL) will be performed using the alkaline hematin method. Starting in Screening, subjects will be dispensed sanitary collection kits that consist of validated sanitary products, product collection bags and a keg with screw-on lid for storage as provided by the vendor.

Validated products have undergone analytical testing by the analytical lab to confirm the following characteristics:

- adequate precision and accuracy of blood recovery
- no or limited interference with the alkaline hematin method

It is important that only the sanitary products provided by the sponsor are used during the study. Validated sanitary products may include:

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

3.22 Return Sanitary Products

Subjects will be required to collect all sanitary products (with or without visible blood) on days with menstrual bleeding or spotting and return them to the clinical study site at visits during the Screening and Treatment periods of the study and at the Premature Discontinuation visit (Section 2). There will be no product collection required during the Follow-up Period.

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.

Menstrual Cycle Product Collection Visit

Subjects will visit the site within approximately 5 days after cessation of bleeding or spotting for Menstrual Cycle Product Collection Visit. Sanitary products to measure MBL will be collected, and the site will submit the sanitary products to the alkaline hematin laboratory for analysis of MBL volume. In addition, a venous blood sample will be obtained and sent with the collected products to the alkaline hematin laboratory. It is recommended that site submit the sanitary products to alkaline hematin laboratory only after verifying that subject has qualifying fibroids per central reader based on the local ultrasound report.

In the event that a subject or study personnel cannot come to the site for venous blood sample collection and return of collected sanitary products because of the COVID-19 pandemic, a home health care service may be utilized to obtain such samples.

If the first screening menstrual cycle does not qualify, an additional screening menstrual cycle may be permitted (Table 2). Screening menstrual Cycle 1 for menstrual bleeding assessment begins with the first day of bleeding or spotting associated with menses.

Table 2 Menstrual Blood Loss Volume Eligibility

Screening Cycle 1 Blood Loss	Screening Cycle 2 Blood Loss	Eligible
> 80 mL	N/A	Yes
≤ 80 mL[a]	> 80 mL	Yes

N/A = not applicable

a. If Screening Cycle 1 blood loss is ≤ 60 mL, study site must consult AbbVie for approval to collect sanitary products for additional menstrual cycles in Screening. Subjects with a Screening Cycle 1 blood loss between > 60 to 80 mL may proceed to collect a second Screening Cycle to determine eligibility without prior approval.

Subjects will be required to collect all sanitary products from the first cycle collected in the Screening period continuously to the end of the placebo-controlled Treatment Period.

Subjects will return their sanitary products to the site at the scheduled on-site visit or at a Product Collection Visit. A Product Collection Visit is only necessary if an on-site visit is not scheduled to occur within approximately 5 days after cessation of bleeding or spotting. Sites should notify the subjects when to start collecting products after they are dispensed the product collection kit on site. This schedule is repeated through the rest of the placebo-controlled Treatment Period.

3.23 Randomization/Drug Assignment

The site will contact Interactive Response Technology (IRT) during the Washout or Screening Period to obtain a subject (Screening) number after the subject has signed the informed consent. Consecutive and unique subject numbers will be assigned and used to identify each subject throughout the study. The registration of the first Screening Visit will trigger shipment of clinical drug supplies to the study site. Subjects will be randomly assigned by IRT to receive either elagolix 150 mg QD or placebo on Day 1; a unique randomization number will be provided via IRT.

During the Treatment Period, sites will register each onsite visit in IRT in order to obtain the appropriate amount of scheduled resupply of study drug to dispense to each subject. In the event study drug becomes lost or damaged, the site can contact IRT to obtain an unscheduled re-supply of study drug kit numbers to dispense to the subject. Sites will register subjects as "Completed" or "Discontinued" (if the subject prematurely discontinues) at the end of the Treatment Period and will also indicate whether the subject will enter the Post-Treatment Follow-Up Period.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of the AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's baseline to Month 6 treatment throughout the study. To maintain the blind, the elagolix and respective matching placebo provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

3.24 Dispense Study Drug

The site will dispense study drug at the time points specified in Section 2.2. The subject will take the first elagolix 150 mg tablet or matching placebo at the study site on Day 1 (randomization) whether the subject's visit is scheduled in the morning or afternoon. Subjects will be instructed to self-administer their study drug throughout the Treatment Period.

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

Sites will be able to utilize Marken and/or another local courier for drug shipment. AbbVie has set up an agreement with Marken (third-party vendor) for sites to use to ship study drug to subjects.

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

The PI must discuss the DTP process with the subject:

- Obtain consent to provide delivery information to Marken and/or local courier and document this in the source.
- Obtain consent to provide delivery information to Marken and/or local courier and document this in the source.
- Confirm that the subject will be available to accept delivery.
- The site will follow up with the subject after shipment is received.
- The subject should maintain the drug containers, as well as any unused drug for return to site.

Sites will be required to retain documentation of the shipment for the IP accountability and monitoring.

3.25 Drug Accountability

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

The IRT will maintain a current and accurate inventory of all clinical drug supplies, accountability, reconciliation, returns, and destruction for each site. The IRT will also include the lot number, kit number, clinical safety system 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.

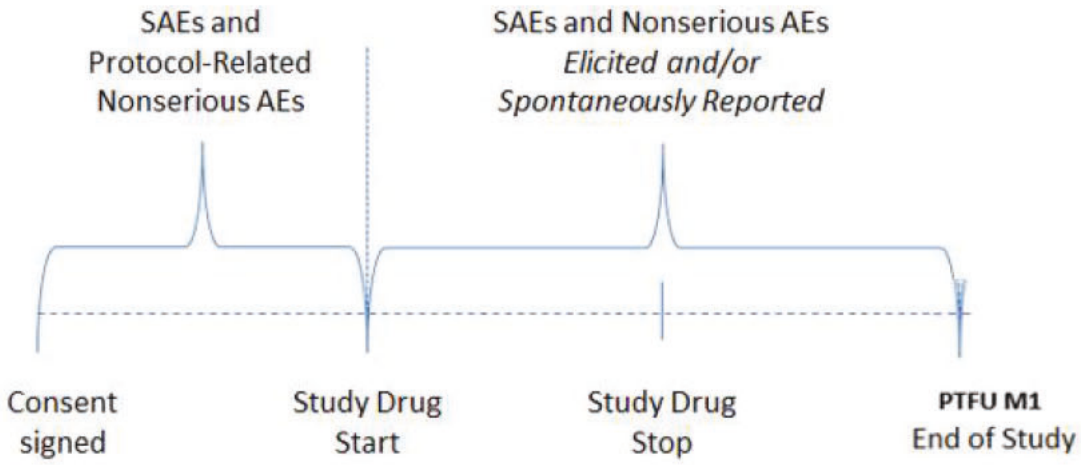
An overall accountability of the study drug will be performed and verified by the site monitor via IRT throughout the study and at the study site closeout visit. Throughout the study and upon completion or termination of the study, all used, unused, and unopened containers will be returned to AbbVie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

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

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

Serious adverse events (SAEs) and protocol-related nonserious AEs will be collected beginning when the subject signs the study-specific informed consent. From the time of study drug administration until PTFU Month 1 visit, all AEs, adverse events of special interests (AESIs), and SAEs will be collected whether solicited or spontaneously reported by the subject.



AE = adverse event; M1 = Month 1; PTFU = Post-Treatment Follow-Up; SAE = serious adverse event

4.2 Recording Data and Analyses of Safety Findings

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (TEAE) (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days after the last dose of study drug) will be tabulated by primary MedDRA system organ class (SOC) and preferred term.

4.3 Reporting Adverse Events and Intercurrent Illnesses

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

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

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

Men's and Women's Health Safety Team
Dept. R48S, Bldg. AP 31-1
1 North Waukegan Road
North Chicago, Illinois 60064
Office: +1 (847) 935-7577
Email: GPRD_SafetyManagement_Hormones@abbvie.com

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
Clinical Development
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office:
Mobile:
Fax:
Email:
[redacted]

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

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for suspected unexpected serious adverse reactions (SUSAR) reporting for the investigational medicinal product (IMP) in accordance with Directive 2001/20/EC.

4.4 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for any study subject with a positive serum pregnancy test after receiving at least one dose of study drug through 30 days following the last dose of study drug. While awaiting serum pregnancy test results during the Treatment Period, study drug should be temporarily discontinued.

If the subject has a positive serum pregnancy test during the Treatment or within 30 days following last dose of study drug, no additional study procedures will be conducted. However, an ultrasound

examination will be performed (read locally) as early as possible during the first trimester of pregnancy to assess gestational age and document intrauterine pregnancy. The following information should be collected: fetal outcome (e.g., spontaneous or elective abortion, live infant, or still birth), date and mode of delivery, birth weight, birth length, gender, any congenital anomaly, and medically significant complications during pregnancy or labor or delivery. For live infant births, information on the health of the infant will be collected from the first post-delivery pediatrician visit and at 6 to 12 months after delivery.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines and Appendix A of the investigator brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the "suspected" serious adverse reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

Subjects will be centrally randomly assigned using an IRT. Subjects randomly assigned to 1 of 2 treatment groups in a 2:1 ratio to receive elagolix 150 mg film-coated tablet or respective matching placebo tablet by oral administration for 6 months in the Double-Blind Treatment Period.

The study drug will be dispensed in the form of tablets at the visits listed in Section 2.2. Study drug should be taken with approximately 8 oz. (240 mL) of water without regard to food and should be taken at approximately the same time each morning to promote compliance. Subjects will be instructed to return all study drug kits (used/unused/unopened) to the study site staff at study visits throughout the Treatment Period or Premature Discontinuation visit (if applicable).

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. Sites should not contact IRT for kit assignment until a subject is onsite for the visit and urine pregnancy test is negative. In the event that a subject cannot come to the site because of the COVID-19 pandemic, the site may contact the IRT for kit assignment after ensuring subject is eligible to continue with study drug dosing and confirming a that a home urine pregnancy test was performed and the result was negative. Study drug dispensing can then be undertaken as outlined in Section 3.24.

6.2 Packaging and Labeling

AbbVie will supply blinded study drug in monthly kits (i.e., cartons) for the 6-month Double-Blind Treatment Period. Study drug is provided at each dispensing visit. The study drug consists of elagolix or

respective matching placebo tablets. Each kit (carton) contains 4 weekly blister cards and 1 extra medication blister card. Each kit supplies sufficient study medication for 4 weeks (28 days) of dosing, plus 1 week of extra medication.

Each individual blister card contains 7 tablets of elagolix or 7 tablets of matching placebo 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 study drug is labeled as per country requirements. All blank spaces on the label will be completed by the site staff prior to dispensing to the subject. Labels must remain affixed to the study drug containers. Adequate supplies of study drug will be provided to each study site automatically via IRT.

Storage and Disposition of Study Drug

Elagolix and respective matching placebo study drug must be stored at controlled temperature 15° to 25°C (59° to 77°F).

The study drug storage temperature must be recorded on each business day. Any temperature excursions must be entered into AbbVie Temperature Excursion Management System (ATEMS) immediately. Study drug should not be dispensed until ATEMS or AbbVie deems the drug as acceptable.

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

6.3 Method of Assigning Subjects to Treatment Groups

This is a randomized, double-blind, 6-month placebo-controlled, parallel-group, multicenter study. Subjects randomized in the Double-Blind Treatment Period will receive elagolix 150 mg or matching placebo for the duration of the Treatment Period.

At the Screening visit, all subjects will be assigned a unique subject number through the use of the IRT. Subjects will be randomly assigned by IRT to receive 1 of the treatments on the Day 1 visit. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the Screening visit throughout the study. After confirming that the subject has met eligibility criteria and prior to the Day 1 (initial randomization dose), a unique randomization number for treatment assignment will be provided via IRT.

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

All randomized subjects will take study drug orally once daily for the entire 6-month Treatment Period at the scheduled visits (Section 2.2). For Day 1 to Month 6, subjects will take a blinded morning dose of elagolix (150 mg) tablet or matching placebo tablet.

7 REFERENCES

1. Spies JB, Coyne K, Guaou Guaou N, et al. The UFS-QoL, a new disease specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet and Gynecol. 2002;99(2):290-6.
2. Columbia-Suicide Severity Rating Scale (C-SSRS) [homepage on the Internet]. Columbia University Medical Center [cited March 9, 2018]. Available from: http://cssrs.columbia.edu/.

APPENDIX A. REASON FOR STUDY PARTICIPATION

M16-824

Date of assessment **Subject Number**

_____ _____ _____ — — — — — — — —
DD MON YYYY

Top portion to be completed by study staff.

Reason for Study Participation

(To be Completed by Study Subject)

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 prefer taking medication without added hormone treatment
- ☐ I would like to get pregnant after participating in the study
- ☐ I don't know why
- ☐ I don't want to answer
- ☐ Other: _____

Subject Initials: _____ Date: _____

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APPENDIX B. PHYSICIAN SURGERY QUESTIONNAIRE (PSQ)

M16-824

Date of assessment **Subject Number**

_____ _____ _____ — — — — — —
DD MON YYYY

Top portion to be completed by study staff.

Physician Surgery Intention Questionnaire
Version 1.0

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 _____

Completed by Physician: _____ Date: _____

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