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Protocol for Study M16-837

Indication: Study of the Safety and Efficacy of Elagolix in Women with Polycystic Ovary Syndrome

VERSION:	4.0	DATE:	02 October 2020
SPONSOR:	AbbVie Inc.*	NUMBER OF SITES:	Approximately 54 sites (United States, including Puerto Rico)
ABBVIE INVESTIGATIONAL PRODUCT:	Elagolix		

FULL TITLE: Phase 2, Multicenter, Double-blind (Sponsor-unblinded), Randomized, Placebo-Controlled Study of the Safety and Efficacy of Elagolix in Women with Polycystic Ovary Syndrome

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

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1 SYNOPSIS

Title: Phase 2, Multicenter, Double-blind (Sponsor-unblinded), Randomized, Placebo-Controlled Study of the Safety and Efficacy of Elagolix in Women with Polycystic Ovary Syndrome	
Background and Rationale:	Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine and metabolic disorder characterized by chronic oligo-anovulation, androgen excess, and polycystic ovaries. Despite being one of the most common hormonal disorders in women of reproductive age, few therapeutic options are available for women with PCOS. Elagolix has the potential to impact the disordered pituitary and ovarian hormonal dynamics in women with PCOS.
Objective and Endpoints:	Objective The objective of the study is to assess the pharmacokinetics, pharmacodynamics, safety, and efficacy of elagolix in women with PCOS. Endpoints Primary Endpoint • The proportion of menstrual cycle responders Key Secondary Endpoint • Change from Baseline to Week 1 in the area under the luteinizing hormone (LH) serum concentration-time curve (AUC). Additional Efficacy Endpoints • Proportion of complete menstrual cycle responders • Change from Baseline in the LH serum AUC at each scheduled assessment during the Treatment Period • Change from Baseline in the follicle-stimulating hormone (FSH) serum AUC at each scheduled assessment during the Treatment Period • Change from Baseline in total and free testosterone serum concentration at each scheduled assessment during the Treatment Period • Number of menstrual bleeding episodes during the Treatment Period • Number of ovulations based on weekly serum progesterone levels during the Treatment Period • Proportion of subjects with at least 2 ovulations during the Treatment Period • Endpoints related to hyperandrogenism – Patient Global Impression (PGI) for both acne and hirsutism; change from Baseline at each scheduled assessment during the Treatment Period for the following: acne measured with total lesion count and investigator's global assessment (IGA), hirsutism measured with Ferriman–Gallwey (FG) score

	• Endpoints related to metabolic features - change from Baseline at each scheduled assessment during the Treatment Period for the following: glycated hemoglobin (HbA1c), fasting insulin/glucose, body mass index (BMI), lipids, waist circumference • Change from Baseline at each scheduled assessment during the Treatment Period for additional hormones: androstenedione, anti-Mullerian hormone (AMH), estradiol (E2), progesterone • Change from Baseline in ovarian volume at each scheduled assessment during the Treatment Period • Endpoints related to the subject's quality of life: change from Baseline in domains from the Polycystic Ovary Syndrome Questionnaire (PCOSQ) (emotions, body hair, weight, infertility problems, and menstrual problems), and the Menstrual Bleeding Questionnaire (MBQ) at each scheduled assessment during the Treatment Period.
Investigators:	Multicenter
Study Sites:	Approximately 54 sites (United States, including Puerto Rico).
Study Population and Number of Subjects to be Enrolled:	Approximately 130 women 18 to 35 years of age with PCOS and a BMI 18.5 to 38 kg/m^2, inclusive
Investigational Plan:	This is a Phase 2, multicenter, randomized, double-blind (sponsor-unblinded), 6-month, placebo-controlled, parallel group study of elagolix in women with PCOS. Eligible subjects will be randomized 2:2:2:2:2:3 (active treatment to placebo) to 25 mg twice daily (BID), 50 mg once daily (QD), 75 mg BID, 150 mg QD, 300 mg QD, or placebo (20 subjects in each active treatment group and 30 subjects in the placebo group).
Key Eligibility Criteria:	Women 18 to 35 years of age with PCOS and a BMI 18.5 to 38 kg/m^2, inclusive
Study Drug and Duration of Treatment:	Elagolix or matching placebo will be administered during the Treatment Period. The duration of the study could be up to 42 weeks, which includes an 8-week Washout (if necessary), a 6-week Screening Period, a 24-week Treatment Period, and a 30-day Post-Treatment Follow-up Period.
Date of Protocol Synopsis:	02 October 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Polycystic ovary syndrome (PCOS) is a complex and heterogeneous endocrine and metabolic disorder characterized by chronic oligo-anovulation, androgen excess, and polycystic ovaries. Despite being one of the most common hormonal disorders in women of reproductive age, few therapeutic options are available for women with PCOS.

Elagolix sodium (hereinafter "elagolix,") is an 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. 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.[1]

Elagolix has the potential to improve the disordered pituitary and ovarian hormonal dynamics in women with PCOS.

Clinical Hypothesis

Elagolix will lower luteinizing hormone (LH) secretion while maintaining follicle-stimulating hormone (FSH) secretion and consequently:

1. Lower serum testosterone concentrations
2. Restore normal menstrual cycles in women with PCOS
3. Improve ovulation
4. Improve hyperandrogenic symptoms

2.2 Benefits and Risks to Subjects

Women with PCOS have symptoms of oligomenorrhea, hirsutism, and anovulation due to excess LH secretion. Elagolix has the potential to improve this symptom complex by reducing LH secretion and potentially restoring a normal LH/FSH ratio. Preliminary data show that at low doses of elagolix, LH is preferentially inhibited compared with FSH. As of 20 August 2018, 4569 subjects have been exposed to elagolix; the safety profile of elagolix is well established even at doses higher than those planned for administration in this study. 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.[1]

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

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of the study is to assess the PK, pharmacodynamics (PD), safety, and efficacy of elagolix in women with PCOS.

3.2 Primary Endpoint

The primary endpoint is the proportion of menstrual cycle responders.

3.3 Key Secondary Endpoint

Change from Baseline to Week 1 in the area under the LH serum concentration-time curve (AUC).

3.4 Additional Endpoints

1. Proportion of complete menstrual cycle responders
2. Change from Baseline in the LH serum AUC at each scheduled assessment during the Treatment Period
3. Change from Baseline in the FSH serum AUC at each scheduled assessment during the Treatment Period
4. Change from Baseline in total and free testosterone serum concentration at each scheduled assessment during the Treatment Period
5. Number of menstrual bleeding episodes during the Treatment Period
6. Number of ovulations based on weekly serum progesterone level during the Treatment Period
7. Proportion of subjects with at least 2 ovulations during the Treatment Period
8. Endpoints related to hyperandrogenism – Patient Global Impression (PGI) for both acne and hirsutism; change from Baseline at each scheduled assessment during the Treatment Period for the following: acne measured with total lesion count and investigator's global assessment (IGA), hirsutism measured with Ferriman–Gallwey (FG) score
9. Endpoints related to metabolic features - change from Baseline at each scheduled assessment during the Treatment Period for the following: glycated hemoglobin (HbA1c), fasting insulin/glucose, body mass index (BMI), lipids, waist circumference
10. Change from Baseline at each scheduled assessment during the Treatment Period for additional hormones: androstenedione, anti-Mullerian hormone (AMH), estradiol (E2), progesterone

11. Change from Baseline in ovarian volume at each scheduled assessment during the Treatment Period
12. Endpoints related to the subject's quality of life: change from Baseline in domains from the Polycystic Ovary Syndrome Questionnaire (PCOSQ) (emotions, body hair, weight, infertility problems, and menstrual problems) and the Menstrual Bleeding Questionnaire (MBQ) at each scheduled assessment during the Treatment Period.

3.5 Safety Endpoints

Safety evaluations include physical examination, vital signs, pelvic ultrasound (includes both transabdominal ultrasound [TAU] and transvaginal ultrasound [TVU]), MRI (if required), clinical laboratory tests (including hematology, chemistry, urinalysis, and lipid panel), bone mineral density (BMD) via dual energy x-ray absorptiometry (DXA) examinations, and adverse event (AE) monitoring for the entire study duration.

3.6 Pharmacokinetic Endpoints

Plasma concentrations of elagolix will be determined at designated visits, and the concentrations may be used to develop a population PK model. The population PK model may be linked with data from the PD endpoints for PK/PD analyses.

3.7 Pharmacodynamic Endpoints

LH and FSH concentrations will be determined at designated visits throughout the study and summarized. Serum $AUC_{0\text{-}t}$ of LH and FSH will be calculated using non-compartmental methods and summarized. Serum concentrations of other endocrine hormones may be determined and summarized if useful for the interpretation of the study results. Additional PD parameters may be calculated if useful in the interpretation of the study results.

3.8 Biomarker Sampling

Optional whole blood, serum, and plasma samples 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 this research is to analyze samples for biomarkers that may help to understand PCOS, related conditions, and the subject's response to elagolix. Research may also include epigenetic changes in deoxyribonucleic acid (DNA) that may associate with the subject's response to treatment or disease. Samples for ribonucleic acid (RNA) may be used to research if any genetic variants result in changes to gene expression. This research is exploratory in nature and the results may not be included with the clinical study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, randomized, double-blind (sponsor-unblinded), 6-month, placebo-controlled, parallel group, multicenter study designed to assess the PK and PD of elagolix and to demonstrate the safety and efficacy of elagolix in women with PCOS.

The duration of the study could be up to 42 weeks, which includes an 8-week Washout (if necessary), a 6-week Screening Period, a 24-week Treatment Period, and a 30-day Post-Treatment Follow-up Period.

The Screening Period may be extended in certain circumstances (e.g., repeat TVU is needed) following consultation with the sponsor.

Study Visits and Assessments: Study visits for safety, efficacy, PK, and PD assessments will be scheduled as listed in the activity schedule (Appendix D). Sites will have the option to participate in sparse PK sampling of elagolix. Optional sparse PK sampling will take place on the scheduled visits at Week 1 and Week 4 of the Treatment Period, as listed on the activity schedule (Appendix D), and includes 5 lab draws over 6 hours. If sites choose not to participate in the optional sparse PK sampling, a single PK sample will be required at the scheduled visits. At other study visits (other than the optional sparse PK sampling study visits), a single PK sample will be collected as per the activity schedule.

Required intensive PD sampling of LH and FSH will occur at Baseline, and the scheduled visits at Week 1, Week 4, and Week 16 of the Treatment Period, as listed on the activity schedule (Appendix D). Required intensive PD sampling includes 7 to 9 lab draws over 3 to 4 hours (taken every 30 minutes). At other study visits (other than intensive PD study visits), a single PD sample will be collected, per the activity schedule.

Washout Period for subjects on oral contraceptives (OCPs): a 2-month Washout Period will be required for subjects who are on OCPs. Washout Period for subjects on metformin: a 1-month Washout Period will be required for subjects on metformin. A full list of Washout Periods for other medications is presented in Table 1.

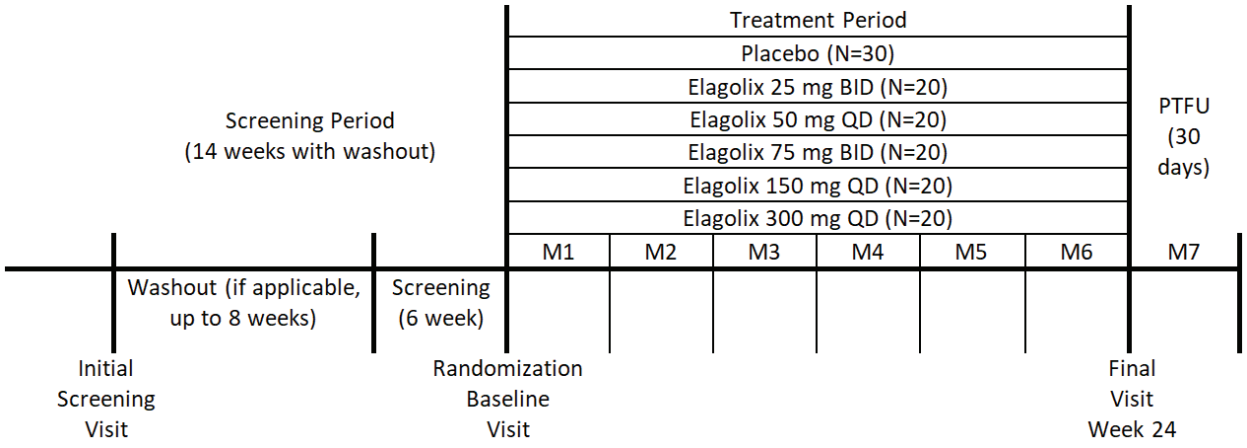
During Screening, subjects will undergo procedures and activities as listed in the Activities Schedule to ensure they meet eligibility requirements.

Beginning at Screening and throughout the Treatment Period, each subject will complete an electronic daily bleeding diary. The subjects will also undergo weekly blood draws for progesterone levels. A progesterone level ≥ 3 ng/mL will be used to indicate ovulation.

Subjects will undergo procedures and activities as listed in the Activities Schedule at the 30-day post-treatment follow-up visit. An unscheduled visit may occur when the subject returns to the clinic at any time for the evaluation of symptoms, changes in concomitant medications, or any AEs.

The study schematic is presented in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F). See Section 5 for information regarding eligibility criteria. Study sites and subjects will remain blinded for the duration of the study.

Figure 1. Study Schematic



BID = twice daily; M = month; PTFU = post-treatment follow-up; QD = once daily

Some of the study visits and visit activities (including but not limited to clinical laboratory tests and concomitant medication assessment) may be conducted in the home or non-hospital/clinic environment by qualified individuals at the investigator's request and with the subject's agreement where local regulation allows.

Rescreening

Subjects who screen fail for this study may be rescreened. Prior to rescreening a subject, the investigator should consult with the AbbVie Therapeutic Area Medical Director (TA MD). The TA MD will determine which procedures will need to be repeated if the subject was a screen failure for this study or another AbbVie elagolix study. The subject must re-consent and meet all eligibility criteria at the time of rescreening to qualify for the study.

4.2 Discussion of Study Design

Choice of Control Group

The control group consists of subjects randomly assigned to receive placebo. No therapy is currently approved for treatment of PCOS.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The safety assessments used in this study are standard and generally recognized as reliable, accurate, and relevant within the context of this study design.

DXA is a standard accepted measure of BMD and will be utilized to assess the effect of elagolix therapy on BMD.

Suitability of Subject Population

Women 18 to 35 years of age with PCOS are selected for this study. The lower age limit (18 years) was chosen based on the youngest adult age; the upper age limit (35 years) was chosen in order to limit the study to women earlier in the disease process. No studies in females outside of the reproductive years are necessary for this proposed indication.

This study will enrich for subjects who have PCOS with menstrual abnormalities and hyperandrogenic features by using criteria for enrollment that require elevated testosterone as well as oligomenorrhea.

Selection of Doses in the Study

The effects of elagolix on gonadotropic and ovarian hormones were evaluated in premenopausal healthy women in 2 Phase 1 studies over 21 days in a multiple-ascending dose study (Study M12-790), and over a period of 3 months in a folliculogenesis study (Study M12-673). In these studies, the evaluated elagolix dosages ranged from 100 mg once daily (QD) to 400 mg twice daily (BID). In the 21-day multiple-ascending dose study, dose-dependent suppression of gonadotropic and ovarian hormones was observed. Based on the results from the 2 studies, elagolix exhibited partial suppression of LH up to 100 mg BID (200 mg total daily dose), and near maximal suppression at 200 mg BID and higher. However, elagolix showed differential FSH suppression compared with LH, where no or minimal suppression was observed up to 200 mg total daily dose and near maximal or maximal suppression at 200 mg BID and higher. In the 3-month folliculogenesis study, ovulatory progesterone concentrations (> 5 nmol/L) were observed more often at lower elagolix dosages (100 to 200 mg QD, 100 mg BID) correlating with higher ovulation rates. In Study M12-790, when the same total daily dose was evaluated as QD or BID (i.e., 100 mg BID versus 200 mg QD), BID regimens appeared to provide more suppression of hormones compared with QD regimens. Testosterone suppression was also observed with elagolix dosages (100 mg BID, 200 mg BID, and 300 mg BID).

Based on the totality of the data from the Phase 1 and exploratory dose-response modeling, a total daily dose range of 50 mg to 300 mg with various dosing regimens (i.e., QD and BID) would provide an opportunity to study and explore a dose range finding in women with PCOS by targeting partial suppression of LH levels without inhibition of FSH and suppressed testosterone to achieve the desired clinical endpoints in women with PCOS. The lowest effective dose that would allow establishment or improvement in menstrual regularity is desired. The upper dose range in the study would also allow evaluation of maximum ability of elagolix to achieve improvement in hyperandrogenic features.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria to be included in the study.

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 any study-specific procedures including washout or screening procedures.

- 2. Subject agrees to the washout intervals for hormonal therapies, including any other medication that may require washout (Table 1) (if a subject has participated in an investigational trial with hormonal treatment, the washout interval applies as listed in Table 1).
- 3. Subject is not taking exclusionary therapies. The medications listed in Table 2 should not be taken during Washout (if applicable), Screening, Treatment Period, and Post-Treatment Follow-up Period.
- 4. Subject must be willing to comply with study-related assessments and procedures, including completion of the daily electronic diary (e-Diary) and avoid use of all hair removal procedures and products throughout the required time periods. Laser hair removal is prohibited throughout the entire duration of the study (see Operations Manual [Appendix F] Section 3.5).

Demographic and Laboratory Assessments

- 5. Adult female, 18 to 35 years of age, inclusive, at the time of Screening.
- 6. Body mass index (BMI) 18.5 to 38 kg/m^2, inclusive at the time of Screening
- 7. A diagnosis of PCOS with subject meeting each of the following historical criteria:
  - Clinical hyperandrogenism or biochemical hyperandrogenism based on physical examination or laboratory findings; and
  - History of ovarian dysfunction indicated by menstrual irregularity: oligomenorrhea (menstrual interval > 35 days or ≤ 8 menstrual cycles per year) or amenorrhea (no menses in 6 consecutive months or greater); and
  - Cycle length > 35 days in the 3 months prior to Baseline based on subject self-report.
- 8. Laboratory values must meet the following criteria within the Screening Period prior to the first dose of study drug:
  - Must not have FSH level > 10 IU/L
  - Elevated testosterone (total testosterone or free testosterone calculated by central laboratory)
  - Aspartate aminotransferase (AST) and alanine aminotransferase (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).
  - Negative urine and/or serum pregnancy test(s) during the Washout (if necessary) and/or Screening Periods, and a negative urine pregnancy test immediately before administration of the first dose of study drug.
  - Subjects must have neither hepatitis B nor C based on the presence of the following:
    - Hepatitis B surface antigen (HBsAg)
    - Hepatitis C virus antibody (HCV Ab) and detectable HCV RNA
    - Equivocal viral test results should be repeated.

- No clinically significant abnormalities in clinical chemistry, hematology, or urinalysis (excluding findings associated with the disease under study).
- Screening labs may be retested once prior to Baseline; for further retesting, contact the TA MD.
- An adequate endometrial biopsy that shows no clinically significant endometrial pathology during Screening (or within 12 months prior to Screening if documentation provided) or endometrial thickness < 5 mm on Screening TVU.
- Must have a normal Papanicolaou (Pap) smear result as described in, Operations Manual (Appendix F), Pap Test Eligibility (applies to subjects ≥ 21 years of age at Screening or age at which Pap smears are routinely performed according to local guidelines).
- Must not have active pelvic inflammatory disease at the time of Screening.

Subject History

- 9. No history of irregular menstrual bleeding associated with conditions other than PCOS (e.g., uterine polyps or submucosal uterine fibroids, adenomyosis)
- 10. Must be more than 6 months post-partum, post-abortion, post-pregnancy, and post-lactation at the time of entry into the Screening Period.
- 11. Must not have had laser hair removal within the 6 months prior to Baseline.
- 12. Must not have clinically significant gynecological finding from screening ultrasound or MRI if required, 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 Baseline and meet eligibility criteria.)
  - Complex ovarian cyst > 3.5 cm in diameter at longest point
  - Large endometrial polyp (≥ 1 cm)
  - Submucosal fibroid
  - Endometrioma > 3.5 cm in diameter (longest diameter)
- 13. Must not be pregnant or breastfeeding or planning a pregnancy until completion of the study.
- 14. Must not have any clinically significant abnormal findings on electrocardiogram (ECG) obtained during Screening.
- 15. No diagnoses of:
  - Cushing's syndrome
  - Late onset congenital adrenal hyperplasia (or elevated screening 17-OH-P); the investigator should determine the applicable reference range for the subject as noted in central laboratory report to determine subject eligibility
  - Androgen-secreting tumors (or total testosterone > 200 ng/dL at Screening)

- Uncontrolled thyroid disease (or abnormal thyroid-stimulating hormone [TSH] and tetraiodothyronine (T4) at Screening)

  *Note: An abnormal TSH will reflex to test T4. If the T4 result is within normal limits, the TSH test can be repeated one time. TSH and T4 must be normal prior to Baseline.
- Hyperprolactinemia (or elevated prolactin at Screening)
- Diabetes mellitus (or abnormal fasting glucose ≥ 126 mg/dL (7.0 mmol/L) or HbA1c values ≥ 6.5 percent (48 mmol/mol) at Screening).
- Major depression or post-traumatic stress disorder episode within 2 years prior to Screening, ***or*** a history of other major psychiatric disorder at any time (e.g., schizophrenia, bipolar disorder).
- Active malignancy or history of malignancy (except basal cell carcinoma of the skin) with or without systemic chemotherapy

16. No osteoporosis or other metabolic bone disease, or any condition that would interfere with obtaining adequate DXA measurements:

- 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).
- History of low-trauma hip or vertebral fractures (e.g., fracture resulting from a fall from a standing height or lower)
- Bilateral hip replacement
- History of spinal surgery, spinal hardware
- Severe scoliosis
- Subject does not meet the limits/specifications of the local DXA machine being used for this study
- Clinically significant hypocalcemia, hypo- or hyperphosphatemia
- Treatment with medication (excluding calcium and vitamin D) for bone disease associated with a decrease in BMD

17. Results of subject's Screening DXA of the lumbar spine (L1 - L4) and total hip/femoral neck must demonstrate adequate BMD as follows:

- Z-score ≥ –2.0

18. No history of:

- A newly diagnosed, clinically significant medical condition requiring therapeutic intervention (e.g., new onset hypertension) that has not been stabilized at least 30 days prior to Baseline
- 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 investigator's opinion (including, but not limited to, uncontrolled hypertension, epilepsy

requiring anti-epileptic medication, unstable angina, confirmed inflammatory bowel disease, hyperprolactinemia, clinically significant infection or injury)

- Drug abuse and/or alcohol abuse within 12 months prior to Screening
- Any suicide attempts ever or answered "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 Baseline.

19. No surgical history of:
    - Hysterectomy
    - Unilateral or bilateral oophorectomy
    - Ovarian wedge resection or ovarian drilling as treatment for PCOS
    - Bariatric surgical procedures of any type within 12 months of Screening
    - Major surgery within 3 months prior to the initial Screening visit
    - Minor surgery within 1 month prior to the initial Screening visit
20. Must not be using:
    - Medications identified in Section 5.3 Table 2 during Washout, Screening, Treatment or Post-Treatment Follow-Up Periods.
    - Copper intrauterine device (CU-IUD), levonorgestrel intrauterine system (LNG-IUS), or implant. If the CU-IUD, LNG-IUS, or implant is removed, and subject completes the required washout if applicable, the subject may be considered for Screening for the study.
    - Systemic corticosteroids for over 14 days within 3 months prior to Screening or anticipate require use of systemic corticosteroids for more than 7 days during the study. Over-the-counter and prescription topical, inhaled, intranasal, or intra-articular (for occasional use) corticosteroids are allowed.
    - Oral retinoid preparations such as Accutane® (isotretinoin) within the last 12 months prior to Screening. Topical isotretinoin applications are also not permitted within the last 28 days prior to Screening.
21. Regarding other study participation, subjects must not be:
    - Previously treated in either an elagolix study or a study involving another investigational GnRH antagonist, within the last 3 months prior to entry into the Screening Period
    - Currently participating in another investigational study (drug or device)
    - Participating in an investigational drug study (i.e., receiving or has received investigational product) within 28 days or 5 times the investigational drug half-life, whichever is longer, prior to Screening procedures

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

Therapy	Minimum Interval for Washout[a]
Medroxyprogesterone acetate injection (Depo Provera®; Sayana®)	12 months from injection
GnRH antagonists and GnRH agonists	3 months
Aromatase inhibitors	3 months
Selective progesterone receptor modulators (e.g., ulipristal acetate, vilaprisan)	3 months
Danazol (Cyclomen®)	
Clomiphene	
Gonadotropins	
Antiandrogens	
Oral, intramuscular or intravenous glucocorticoids	
Oral contraceptives[b]	2 months
Oral, transdermal, or intravaginal estrogen preparations	
Oral, intravaginal or transdermal progesterone/progestin preparations, including tibolone	
Hormonal and nonhormonal IUD, sub-dermal progestin implant (e.g., Nexplanon®)	2 months after removal
NuvaRing®	
Moderate (bosentan, efavirenz, etravirine, modafinil) or strong inducers (phenytoin, rifampin, carbamazepine, St. John's Wort, mitotane) of cytochrome P450 3A (CYP3A) Moderate (cimetidine, ciprofloxacin, erythromycin, fluconazole) or strong (itraconazole, ketoconazole, grapefruit juice, clarithromycin, diltiazem) inhibitors of CYP3A	1 month
Metformin (and other insulin-sensitizing agents)	
Statins (and other lipid-lowering agents)	

GnRH = gonadotropin-releasing hormone; IUD = intrauterine device

a. This is the minimum washout. If less than a full course of therapy is administered, the investigator should contact the AbbVie TA MD listed on the cover page of this protocol to discuss and confirm the required washout interval.

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

5.2 Contraception

Subject must agree to the use of at least 2 forms of nonhormonal contraception (dual contraception) consistently throughout the Washout (if applicable), Screening, Treatment Period, and Post-Treatment Follow-Up 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).
- Vaginal sponge impregnated with spermicide used with a condom.

Subject is not required to use dual contraception methods if:

- Sexual partner(s) is vasectomized at least 6 months prior to Screening or is documented to be sterile for any reason.
- 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 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 Washout (if applicable), Screening, Treatment Period, and Post-Treatment Follow-Up Period.

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®) GnRH antagonists (other than study drug)
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, intrauterine device (IUD), or LNG-IUS, except emergency contraception) hCG or hCG products Levonorgestrel (except emergency contraception, i.e., levonorgestrel 1.5 mg) Glucocorticoids, oral or injectable (chronic use only) Spironolactone and other antiandrogens Aromatase inhibitors Infertility treatments Clomiphene 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)
Treatments for impaired glucose tolerance and diabetes	Metformin or other similar medications, including diabetes treatments
Statins (and other lipid-lowering agents)	

Prohibited During the Washout, Screening, and Treatment Periods	
Moderate and strong CYP3A inhibitors such as:	Moderate Inhibitors: Cimetidine Ciprofloxacin Erythromycin Fluconazole Strong Inhibitors: Itraconazole Ketoconazole Grapefruit juice Clarithromycin Diltiazem
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 inhibitors of organic anion transporter peptide (OATP) 1B1, such as:	Cyclosporine Rifampin (single dose)
Oral and topical retinoids, teratogens, such as:	Isotretinoin (Accutane®), and other oral as well as topical retinoids
Any drug known to affect bone density	Examples include first-generation antiepileptic drugs, Topiramate
Prohibited During the Screening, Treatment, and Post-Treatment Follow-Up Periods	
Osteoporosis medications bisphosphonates, RANKL, [receptor activator of nuclear factor-κ B ligand] inhibitors, anabolic bone agents, or rPTH, such as:	Denosumab, teriparatide, Fosamax®, Fosamax Plus D®, Binosto®, Boniva®, Reclast®, Zometa®, Prolia®, XGEVA®, Forteo®, Actonel®, Atelvia®, Miacalcin®, Fortical®
Synthetic prostaglandin E1 (PGE1) analogs, such as:	Misoprostol (Cytotec®, Arthrotec®) Single use of PGE1 for cervical preparation prior to biopsy is allowed; chronic use is prohibited.
Glucocorticoids/corticosteroids, systemic administration (oral, IM, or IV)	*Except for short-term use as noted in this protocol. See Section 5.1.*

Any oral acne treatments and topical acne medications, such as:	Oral antibiotics, topical retinoids, benzoyl peroxide

CYP3A = cytochrome P450 3A isoform subfamily; GnRH = gonadotropin-releasing hormone; hCG = human chorionic gonadotropin; IM = intramuscular; IV = intravenous; LNG-IUS = levonorgestrel intrauterine system; OATP = organic anion transporting polypeptide; rPTH = recombinant human parathyroid hormone

5.4 Prior and Concomitant Therapy

Any medication administered to treat PCOS symptoms within 6 months prior to Washout or Screening must be recorded in source documents and in the electronic case report forms (eCRFs). The date(s) of administration (including start and stop dates), dose, frequency, route, and reason for use and discontinuation must be recorded in source documents and on the appropriate eCRF.

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

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies. Information regarding potential drug interactions with elagolix can be located in the elagolix Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or up to 8 weeks prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD.
- Clinically significant deterioration of the subject's medical status as determined by the investigator.
- Any other medical reason that AbbVie or the investigator deems appropriate.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study for any reason.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.

- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant or has a positive serum pregnancy test.
- The subject experiences a nontraumatic bone fracture.
- In the investigator's opinion, the subject is unable or unwilling to comply with study-related assessments and procedures, including completion of the e-Diary.
- If any of the following hepatic function test criteria is met, study drug must be discontinued:
  - AST and/or ALT elevations > 8 × upper limit of normal (ULN)
  - AST and/or ALT elevations > 5 × ULN for more than 2 weeks
  - AST and/or ALT elevations > 3 × ULN, with total bilirubin > 2 × ULN
  - AST and/or ALT elevations > 3 × ULN, accompanied by clinical signs or symptoms suggestive for hepatic injury (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [> 5%]).

  Isolated lab abnormalities in an otherwise well-appearing subject should be confirmed prior to study drug discontinuation. A thorough investigation of potential etiologies for the elevated transaminases should be conducted (e.g., trauma, acetaminophen use, viral hepatitis, alcohol ingestion), and the subject should be followed closely for clinical progression.

  Subjects for whom treatment is discontinued for elevated hepatic function tests should have transaminases and bilirubin levels repeated by the central laboratory within 48 to 72 hours of the initial finding if possible and then be monitored closely until levels normalize or return to Baseline.

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.

Discontinuation of Study

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. If, in the judgment of the investigator and AbbVie, the continued exposure to the study drug represents an unexpected, significant, or unacceptable risk to subjects, the study will be stopped. An example of such risk would be if 3 or more subjects developed active liver disease, as defined in the discontinuation criteria above.

Treatment Interruption

AbbVie or the investigator may request that a subject temporarily discontinue study drug administration, which will be referred to as "treatment interruption." The following are examples for reasons when the AbbVie TA MD must be notified in order to assess whether a subject should undergo temporary treatment interruption:

- Adverse event, that based on clinical judgment, requires temporary suspension of treatment or prevents a subject from taking study drug
- 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).

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

The investigator should contact the AbbVie medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix F for details on how to handle study activities/procedures.

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 continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

All attempts must be made to determine the date of the last study drug dose and the reason for discontinuation of study drug 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

Subjects will be randomly assigned to elagolix or matching placebo.

The treatment administration is presented in Table 3.

Table 3. Treatment Administered

	Investigational Product				
Treatment Group	**Dosing Time**	**Elagolix 25 mg Capsule**	**Elagolix 75 mg Capsule**	**Elagolix 150 mg Capsule**	**Matching Placebo Capsule**
Elagolix 25 mg BID	AM	1	0	0	1
	PM	1	0	0	0
Elagolix 50 mg QD	AM	2	0	0	0
	PM	0	0	0	1
Elagolix 75 mg BID	AM	0	1	0	1
	PM	0	1	0	0
Elagolix 150 mg QD	AM	0	0	1	1
	PM	0	0	0	1
Elagolix 300 mg QD	AM	0	0	2	0
	PM	0	0	0	1
Placebo	AM	0	0	0	2
	PM	0	0	0	1

BID = twice daily; QD = once daily

The study drug, consisting of elagolix 25 mg, 75 mg, 150 mg capsules (identical in appearance), or respective matching placebo capsules, will be supplied in a carton with 5 blister cards. Subjects will be instructed to self-administer their study drug.

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 25 mg hard gelatin capsule Elagolix 75 mg hard gelatin capsule Elagolix 150 mg hard gelatin capsule	Universal placebo hard gelatin capsule
Active Ingredient	Elagolix	N/A
Mode/Route of Administration	Oral	Oral
Formulation	RC2 tablet over-encapsulated in Size #0 hard gelatin capsule shells	N/A
Dosage Form	Hard Gelatin Capsule	Hard gelatin capsule
Dose and Units	25 mg, 75 mg, and 150 mg	Universal placebo capsule
Drug Preparation/Packaging	Blister card	Blister card
Blinding	Blinded, capsules	Blinded, capsules
Frequency of Administration	50 mg, 150 mg, 300 mg: QD 25 mg, 75 mg: BID	Matching placebo regimen
Storage Conditions	15 to 25°C	15 to 25°C

BID = twice daily; N/A = not applicable; QD = once daily; RC2 = roller compaction 2

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject and direct-from-patient (DFP) transfer will be available if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix F for details on DTP shipment of study drug.

Compliance

During the Treatment Period visits or Premature Discontinuation visit, the subject will be asked to confirm whether doses were taken and to provide the dates and approximate times of the last 4 doses of study drug prior to elagolix PK samples as noted in Appendix D, Activity Schedule. 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 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, Activity Schedule.

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. For subjects who rescreen, the screening number assigned by the IRT at the initial washout or screening visit should be used.

Once the subject's eligibility has been confirmed and prior to the Baseline (randomization) dose, a unique randomization number will be provided via IRT. Stratified Randomization will be performed by a ratio of 2:2:2:2:2:3 to the following treatments: 25 mg BID, 50 mg QD, 75mg BID, 150 mg QD, 300 mg QD, or placebo (20 subjects in each active treatment group and 30 subjects in the placebo group). Subject randomization will be stratified based on FG score (< 8, ≥ 8) and BMI (< 30, ≥ 30).

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

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

Breaking Blind

Blind break transaction is performed in the study IRT system. 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, including those that may be due to the COVID-19 pandemic), 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 can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

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 AE can result from use of the drug as stipulated in the protocol or approved labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. 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.

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 or contract research organization (CRO) (as appropriate) as an SAE within 24 hours of the site's being made aware of the SAE (refer to Section 4.3 of the Operations Manual 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.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

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.

Adverse events 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 AEs of special interest will be monitored during the study:

- Elevated hepatic transaminases
- BMD decrease/fractures
- Mood and depression-related events

Of note, all pregnancy outcomes will be monitored (see below).

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE as mild, moderate, or severe.

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 after the site becomes aware of the pregnancy. Subjects who become pregnant after receiving at least one dose of study drug during the Treatment Period or within 30 days of last dose of study drug of the

study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

If a subject has a positive serum pregnancy test during the Treatment Period, no additional 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.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Study sites and subjects will remain blinded for the duration of this double-blind study. The sponsor, however, will be unblinded for the entirety of the study.

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The full analysis set (FAS) consists of all randomly assigned subjects who have received at least one 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 the 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 consists of all subjects who received at least one dose of study drug. The data from the safety analysis set will be presented by the treatment actually received no matter what treatment group was assigned at the time of randomization. If a subject takes more than one treatment, the subject will be analyzed in the safety analysis set as taking the treatment to which she was randomized. All safety analyses will be performed based on the safety analysis set.

7.3 Statistical Analyses for Efficacy

Primary Analysis

The primary endpoint is the proportion of menstrual cycle responders. A subject is considered a menstrual cycle responder if she has at least 2 normal menstrual cycles during the final 4 months of the Treatment Period. In addition, a subject is considered a complete menstrual cycle responder if she has normal menstrual cycles beginning at or before Month 3 that are maintained through Month 6 during the Treatment Period. The proportion of complete menstrual cycle responders will be considered an additional endpoint.

For the primary efficacy endpoint, the pairwise comparisons for the difference in proportion of responders between each treatment group and placebo group will be analyzed using the Cochran-Mantel-Haenszel test (CMH) adjusted for FG score (< 8, ≥ 8) and BMI (< 30, ≥ 30) at Baseline. Additionally, the CMH-based 95% confidence interval for the difference in proportion of responders within each FG score (< 8, ≥ 8) and BMI (< 30, ≥ 30) at Baseline will be calculated based on normal approximation.

The primary analysis will be based on observed cases only; missing data will not be imputed for the primary endpoint.

Details on the primary and other efficacy analyses are provided in the SAP.

Sample Size Estimation

Approximately 130 subjects: 20 subjects per elagolix treatment group and 30 subjects assigned to placebo.

The sample size will provide at least 85% power to detect a difference between each elagolix group and the placebo group in the proportion of menstrual cycle responders, assuming response rates of 10% for the placebo group and 50% for the elagolix group with 2-sided $\alpha = 0.05$. The above sample size was calculated using nQuery advisor 7.0.

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
- A summary of DXA results

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

8 ETHICS

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

The protocol, ICF(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(s) 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.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to the Operations Manual in Appendix F for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

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

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

1. AbbVie. Elagolix Investigator's Brochure.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
17-OH-P	17-OH-progesterone
AE	Adverse event
AGC	Atypical glandular cells
ALT	Alanine aminotransferase
AMH	Anti-Mullerian hormone
ASC-H	Atypical squamous cells cannot exclude HSIL
ASC-US	Atypical squamous cells of undetermined significance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BID	Twice daily
BMD	Bone mineral density
BMI	Body mass index
CIN	Cervical intraepithelial neoplasia
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease-2019
CRF	Case report form
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CU-IUD	Copper intrauterine device
DHEAS	Dehydroepiandrosterone sulfate
DNA	Deoxyribonucleic acid
DFP	Direct-from-patient
DTP	Direct-to-patient
DXA	Dual energy X-ray absorptiometry
E2	Estradiol
ECG	Electrocardiogram
eCRF	Electronic case report form
EC/TZ	Endocervical/transformational zone
EDC	Electronic data capture
FAS	Full analysis set

FG	Ferriman–Gallwey
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C virus antibody
HDL-C	High-density lipoprotein cholesterol
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IGA	Investigator's global assessment
IRB	Institutional review board
IRT	Interactive response technology
IUD	Intrauterine device
LDL-C	Low-density lipoprotein cholesterol
LH	Luteinizing hormone
LNG-IUS	Levonorgestrel intrauterine system
LSIL	Low-grade squamous intraepithelial lesion
MBQ	Menstrual Bleeding Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
NILM	Negative intraepithelial lesion or malignancy
OCPs	Oral contraceptives
Pap	Papanicolaou
PCOS	Polycystic ovary syndrome
PCOSQ	Polycystic Ovary Syndrome Questionnaire
PD	Premature discontinuation/Pharmacodynamic(s)
PGI	Patient Global Impression
PK	Pharmacokinetic(s)
QD	Once daily
RNA	ribonucleic acid
RSI	Reference safety information

SAE	Serious adverse event
SAP	Statistical analysis plan
SHBG	Sex hormone binding globulin
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reactions
T4	tetraiodothyronine
TA MD	Therapeutic Area Medical Director
TAU	Transabdominal ultrasound
TSH	Thyroid-stimulating hormone
TVU	Transvaginal ultrasound
ULN	Upper limit of normal
USA	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-837: Phase 2, Multicenter, Double-blind (Sponsor-unblinded), Randomized, Placebo-Controlled Study of the Safety and Efficacy of Elagolix in Women with Polycystic Ovary Syndrome

Protocol Date: 02 October 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
		Clinical Development
		Clinical Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology and Pharmacometrics
		Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The required study activities are shown in the following table. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed within the Operations Manual (Appendix F).

Study Activities Table

Activity	Washout (if applicable) and Screening period		Treatment Period								
	Washout period	Screening	Baseline	Week 1	Week 2 and Week 3 (lab only)	Week 4	Week 5, Week 6, and Week 7 (lab only)	Week 8	Week 9, Week 10, and Week 11 (lab only)	Week 12	Week 13, Week 14, and Week 15 (lab only)
INTERVIEWS & QUESTIONNAIRES											
Subject information and Informed consent	✓	✓									
Eligibility criteria	✓	✓	✓								
Medical/surgical history	✓	✓	✓								
Alcohol, nicotine, and drug use	✓	✓	✓								
Gynecological/obstetrical history	✓	✓	✓								
Birth control attestation			✓			✓		✓		✓	
Contraceptive counseling/dispense nonhormonal contraceptives as necessary	✓	✓	✓	✓		✓		✓		✓	
Adverse event assessment	✓	✓	✓	✓		✓		✓		✓	
PCOSQ			✓					✓			
CSSRS – Baseline/Screening		✓	✓								
CSSRS – Since Last Visit						✓		✓		✓	
Menstrual Bleeding Questionnaire (MBQ)			✓					✓			

Activity	Washout (if applicable) and Screening period		Treatment Period								
	Washout period	Screening	Baseline	Week 1	Week 2 and Week 3 (lab only)	Week 4	Week 5, Week 6, and Week 7 (lab only)	Week 8	Week 9, Week 10, and Week 11 (lab only)	Week 12	Week 13, Week 14, and Week 15 (lab only)
Patient Global Impression of Acne and Hirsutism (PGIA and PGIH)								✓			
Prior/concomitant therapy	✓	✓	✓	✓		✓		✓		✓	
Dispense e-Diary and begin e-Diary daily entry		✓									
Review e-Diary entries			✓	✓		✓		✓		✓	
LOCAL LABS & EXAMS											
Height		✓									
Weight and waist circumference		✓	✓			✓		✓			
12-lead ECG		✓									
Vital signs	✓	✓	✓			✓		✓			
Physical examination		✓	✓								
Gynecological (pelvic and breast) examination		✓									
Pap test (if needed)		✓									
FG Score			✓					✓			
Acne lesion assessment and Investigator's Global Assessment (IGA)			✓			✓		✓			
Pelvic ultrasound (TVU and TAU)		✓				✓		✓			
MRI (if required)		✓									
Endometrial biopsy (if required)		✓									
Urine pregnancy test	✓	✓	✓			✓		✓		✓	
DXA scan		✓									

Activity	Washout (if applicable) and Screening period		Treatment Period								
	Washout period	Screening	Baseline	Week 1	Week 2 and Week 3 (lab only)	Week 4	Week 5, Week 6, and Week 7 (lab only)	Week 8	Week 9, Week 10, and Week 11 (lab only)	Week 12	Week 13, Week 14, and Week 15 (lab only)
CENTRAL LABS											
Clinical laboratory tests • Chemistry (see below for liver function tests and bilirubin) • Lipid panel • Hematology • Urinalysis		✓	✓			✓		✓			
Serology (Hepatitis B and C screens)		✓									
Liver transaminases (ALT, AST) and fractionated bilirubin		✓	✓			✓		✓		✓	
Serum pregnancy test			✓							✓	
Optional sparse PK sampling of elagolix (Week 1 and Week 4 only)				✓		✓					
Intensive PD sampling of LH, FSH			✓	✓		✓					
Screening endocrine tests • FSH • DHEAS • Reflexive thyroid-stimulating hormone (TSH) • Prolactin • 17-OH-P • Fasting insulin • HbA1c		✓									

Activity	Washout (if applicable) and Screening period		Treatment Period								
	Washout period	Screening	Baseline	Week 1	Week 2 and Week 3 (lab only)	Week 4	Week 5, Week 6, and Week 7 (lab only)	Week 8	Week 9, Week 10, and Week 11 (lab only)	Week 12	Week 13, Week 14, and Week 15 (lab only)
Endocrine hormones/test: • Fasting Insulin • HbA1c (Baseline, Week 12, and Week 24) • Androstenedione • AMH			✓			✓		✓		✓	
Testosterone/SHBG, E2		✓	✓			✓		✓		✓	
Progesterone		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Elagolix single PK sample				✓		✓		✓		✓	
LH/FSH single PD sample								✓		✓	
Optional biomarker samples			✓					✓			
℞ TREATMENT											
Randomization/drug assignment			✓								
Dispense study drug			✓			✓		✓		✓	
Review subject dosing and perform drug reconciliation						✓		✓		✓	

Activity	Treatment Period					Post-Treatment Follow-up Period	
	Week 16	Week 17, Week 18, and Week 19 (lab only)	Week 20	Week 21, Week 22, and Week 23 (lab only)	Week 24/PD	30-day Follow-up	Unscheduled Visit
INTERVIEWS & QUESTIONNAIRES							
Contraceptive counseling/dispense nonhormonal contraceptives as necessary	✓		✓		✓		✓
Birth control attestation	✓		✓		✓		✓
Adverse event assessment	✓		✓		✓	✓	✓
Review e-Diary entries	✓		✓		✓		
PCOSQ	✓				✓		
CSSRS – Since Last Visit	✓		✓		✓		
MBQ	✓				✓		
PGIA and PGIH	✓				✓		
Concomitant therapy	✓		✓		✓	✓	✓
LOCAL LABS & EXAMS							
Weight and waist circumference	✓				✓		✓
Vital signs	✓				✓		✓
Physical examination					✓		
Gynecological (pelvic and breast) examination					✓		

Activity	Treatment Period					Post-Treatment Follow-up Period	
	Week 16	Week 17, Week 18, and Week 19 (lab only)	Week 20	Week 21, Week 22, and Week 23 (lab only)	Week 24/PD	30-day Follow-up	Unscheduled Visit
FG Score	✓				✓		
Acne lesion assessment and Investigator's Global Assessment (IGA)	✓				✓		
Pelvic ultrasound (TVU and TAU)	✓				✓		
MRI (if required)					✓		
Urine pregnancy test	✓		✓		✓		✓
DXA Scan					✓		
CENTRAL LABS							
Clinical Laboratory Tests • Chemistry (see below for liver function tests and bilirubin) • Lipid panel • Hematology • Urinalysis	✓				✓		✓
Liver transaminases (ALT, AST) and fractionated bilirubin	✓		✓		✓		
Serum pregnancy test					✓	✓	
Intensive PD Sampling of LH, FSH	✓						

Activity	Treatment Period					Post-Treatment Follow-up Period	
	Week 16	Week 17, Week 18, and Week 19 (lab only)	Week 20	Week 21, Week 22, and Week 23 (lab only)	Week 24/PD	30-day Follow-up	Unscheduled Visit
Endocrine hormones/test: • Fasting Insulin • HbA1c (Screening, Baseline, Week 12, and Week 24) • Androstenedione • AMH	✓				✓	✓	
Progesterone	✓	✓	✓	✓	✓	✓	✓
Testosterone/SHBG, E2	✓		✓		✓	✓	✓
Elagolix single PK sample	✓		✓		✓		
LH/FSH single PD sample			✓		✓	✓	
Optional biomarker samples					✓		
℞ TREATMENT							
Dispense study drug	✓		✓				
Review subject dosing and perform drug reconciliation	✓		✓		✓		

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	11 January 2019
Version 2.0	02 May 2019
Version 3.0	21 October 2019

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol and Operations Manual, and to clarify information in addition to the following:

- Remove "at time of diagnosis" in Protocol Section 5.1, eligibility criterion 7

  Rationale: Physical examination or laboratory findings documenting clinical hyperandrogenism or biochemical hyperandrogenism can be documented during screening, not necessarily at the time of diagnosis.

- Remove "Bilateral tubal ligation, bilateral tubal occlusion, or bilateral salpingectomy" in Protocol Section 5.1, eligibility criterion 19

- **Rationale:** Subjects are required to use 2 nonhormonal forms of contraception in this study. Bilateral tubal ligation, bilateral tubal occlusion or bilateral salpingectomy are forms of nonhormonal permanent contraception; therefore, these subjects will not be excluded from the study.

- Add procedures related to breaking the blind in Protocol Section 5.8

  Rationale: Clarification that the blind break transaction is performed in the study IRT system.

- Add sampling windows for PK and PD samples to Section 3.6 and Section 3.7, respectively, in the Operations Manual

  Rationale: Sampling windows were added to define acceptable times of serial sample collections to provide sites flexibility in performing sparse PK sampling and intensive PD sampling.

- Add directions for protocol modifications related to the coronavirus disease-2019 (COVID-19) pandemic in Protocol Section 2.2, Section 5.5, Section 5.7, Section 5.9, Section 8.2, Section 9, and Appendix D, and to Operations Manual Section 2, Section 2.2, Section 3.1, Section 3.5, Section 3.6, Section 3.7, Section 3.8, Section 3.9, Section 3.11, Section 3.12, Section 3.13, Section 3.14, Section 3.17, Section 3.18, Section 3.19, Section 4.4, and Section 6.1, to describe alternative processes that may be needed.

  Rationale: To 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 M16-837

Indication: Study of the Safety and Efficacy of Elagolix in Women with Polycystic Ovary Syndrome

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Elagolix

FULL TITLE: Phase 2, Multicenter, Double-blind (Sponsor-unblinded), Randomized, Placebo-Controlled Study of the Safety and Efficacy of Elagolix in Women with Polycystic Ovary Syndrome

1 CONTACTS

Sponsor/Therapeutic Area Medical Director (TA MD)/ Emergency Medical Contact	[redacted] AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office: Mobile: Fax: Email: [redacted]
Safety Concerns	Men's and Women's Health Safety Team Dept. R48S, Bldg AP31 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 847-935-7577 Email: GPRD_SafetyManagement_Hormones@abbvie.com
SAE Reporting outside of RAVE	Pharmacovigilance	Fax: +1 847-938-0660 Email: PPDINDPharmacovigilance@abbvie.com
Protocol Deviations	[redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064 ***or***	Office: Fax: Email: [redacted] ***or***
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Certified Clinical Lab	Covance CLS 8211 SciCor Drive Indianapolis, IN 46214	Phone: +1 866-762-6209
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Exploratory 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

Study visits may be impacted due to the coronavirus disease-2019 (COVID-19) pandemic. This may include changes such as phone or virtual site visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in updates throughout this Operations Manual. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates throughout this Operations Manual on how to proceed.

2.1 Individual Washout/Screening Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Washout/Screening Period Activity Schedule.

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

WASHOUT:

INTERVIEW	• Subject informed consent • Eligibility criteria • Medical/surgical history (including alcohol, nicotine, and drug use)	• Gynecological/obstetrical history • Adverse event (AE) assessment • Prior and/or concomitant therapy • Contraceptive counseling/dispense nonhormonal contraceptives as necessary
EXAM	• Vital signs • Urine pregnancy test	

SCREENING:

INTERVIEW	• Subject informed consent • Eligibility criteria • Medical history (including alcohol, nicotine, and drug use) • Gynecological/obstetrical history • AE assessment	• Prior/concomitant therapy • Contraceptive counseling/dispense nonhormonal contraceptives as necessary
PRO	• Dispense electronic diary (e-Diary) and begin daily e-Diary	• Columbia Suicide Severity Rating Scale (C-SSRS) Screening
EXAM	• 12-lead electrocardiogram (ECG) • Height, weight, and waist circumference • Vital signs • Papanicolaou (Pap) test (if needed) • Urine pregnancy test • Physical examination • Gynecological (pelvic and breast) examination	• Magnetic resonance imaging (MRI) if required • Pelvic ultrasound (transvaginal ultrasound [TVU] and transabdominal ultrasound [TAU]) • Endometrial biopsy (if required) • Dual energy X-ray absorptiometry (DXA) scan

CENTRAL LAB	• Clinical laboratory tests (chemistry, hematology, lipid panel, urinalysis)
	• Liver transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and fractionated bilirubin
	• Screening endocrine hormones/test:
	  • Follicle-stimulating hormone (FSH)
	  • Dehydroepiandrosterone sulfate (DHEAS)
	  • Reflexive thyroid-stimulating hormone (TSH)
	  • Prolactin
	  • 17-OH-progesterone (17-OH-P)
	  • Fasting insulin
	  • Glycated hemoglobin (HbA1c)
		• Endocrine hormones:
		  • Testosterone/sex hormone binding globulin (SHBG)
		  • Estradiol (E2)
		  • Progesterone
		• Serology (hepatitis B and C) screens

NOTES: Pap test will be performed in subjects ≥ 21 years of age during the Screening Period only if the subject has not had a Pap test or colposcopy within 6 months of the Screening visit and documentation is present to confirm eligibility as outlined in Figure 1 Pap Test Eligibility. Endometrial biopsy will be performed only if it has not been performed within 12 months of the Screening visit and documentation is

present to confirm eligibility. Results of the endocrine hormones/test must be received and reviewed by site for eligibility prior to Baseline.

2.2 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

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

Scheduled monthly visits during the Treatment Period are based on a 28-day month. All scheduled visits after Baseline through Week 4 should occur within ± 1 day of the projected date. All scheduled visits after Week 4 should occur within ± 3 days of the projected date. However, the TVU and DXA scan may be performed within approximately ± 15 days around the scheduled 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.

BASELINE: 

INTERVIEW	• Eligibility criteria • Medical history (including alcohol, nicotine, and drug use) • Gynecological/obstetrical history • AE assessment • Prior/concomitant therapy	• Birth control attestation • Contraceptive counseling/ dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS – Baseline • Menstrual Bleeding Questionnaire (MBQ)	• Polycystic Ovary Syndrome Questionnaire (PCOSQ)
EXAM	• Physical examination • Weight and waist circumference • Vital signs • Urine pregnancy test	• Acne lesion assessment and Investigator's global assessment (IGA) • Ferriman-Gallwey (FG) score

CENTRAL LAB	• Serum pregnancy test
	• Clinical laboratory tests (chemistry, hematology, lipid panel, urinalysis)
	• Liver transaminases (ALT, AST) and fractionated bilirubin
	• Endocrine hormones/test:
	  • Fasting Insulin
	  • HbA1c
	  • Testosterone/SHBG
	  • Androstenedione
	  • Anti-Mullerian hormone (AMH)
	  • Estradiol (E2)
	  • Progesterone
		• Optional biomarker sample: whole blood (deoxyribonucleic acid [DNA] and ribonucleic acid [RNA]), serum, plasma
		• Intensive PD sampling of luteinizing hormone (LH), FSH

TREATMENT	• Randomization/drug assignment	• Dispense study drug

NOTE: Study drug should begin the morning after Baseline visit. Site should remind subject 2 weeks prior to FG score to avoid use of all hair removal procedures and products.

WEEK 1:

INTERVIEW	• AE assessment • Prior/concomitant therapy	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
CENTRAL LAB	• Optional sparse pharmacokinetic (PK) sampling of elagolix • Intensive pharmacodynamics (PD) sampling of LH, FSH	• Elagolix single PK sample • Endocrine hormones: • Progesterone

NOTE: If sites do not participate in the optional sparse PK sampling, they will be required to provide a single a sample at this visit.

WEEKS 2 AND 3 (Lab Only):

CENTRAL LAB	• Endocrine hormones: • Progesterone

WEEK 4:

INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS Since Last Visit	
EXAM	• Weight and waist circumference • Vital signs • Acne lesion assessment and IGA	• Pelvic ultrasound (TVU and TAU) • Urine pregnancy test

CENTRAL LAB	• Endocrine hormones:
	  • Fasting insulin
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
	• Optional sparse PK sampling of elagolix
	• Intensive PD sampling of LH, FSH
		• Clinical laboratory tests (chemistry, hematology, lipid panel, urinalysis)
		• Liver transaminases (ALT, AST) and fractionated bilirubin

TREATMENT	• Dispense study drug	• Review subject dosing and perform drug reconciliation

NOTE: If sites do not participate in the optional sparse PK sampling, they will be required to provide a single PK sample at this visit.

WEEKS 5, 6, AND 7 (Lab Only):

CENTRAL LAB	• Endocrine hormones: • Progesterone

WEEK 8:

INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS Since Last Visit • MBQ	• PCOSQ • PGIA and PGIH
EXAM	• Weight and waist circumference • Vital signs • Acne lesion assessment and IGA • FG Score	• Pelvic ultrasound (TVU and TAU) • Urine pregnancy test

CENTRAL LAB	• Endocrine hormones:
	  • Fasting insulin
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
	• Elagolix single PK sample
	• LH/FSH single PD sample
		• Clinical laboratory test (chemistry, hematology, lipid panel, urinalysis)
		• Liver transaminases (ALT, AST) and fractionated bilirubin
		• Optional biomarker sample: whole blood (DNA and RNA), serum, plasma

TREATMENT	• Dispense study drug	• Review subject dosing and perform drug reconciliation

NOTE: Site should remind subject 2 weeks prior to FG score to avoid use of all hair removal procedures and products.

WEEKS 9, 10, AND 11 (Lab Only):

CENTRAL LAB	• Endocrine hormones: • Progesterone

WEEK 12:		
INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS Since Last Visit	
EXAM	• Urine pregnancy test	

CENTRAL LAB	• Endocrine hormones/test:
	  • Fasting insulin
	  • HbA1c
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
	• Liver transaminases (ALT, AST) and fractionated bilirubin
		• Elagolix single PK sample
		• LH/FSH single PD sample
		• Serum pregnancy test

TREATMENT	• Dispense study drug	• Review subject dosing and perform drug reconciliation

WEEKS 13, 14, AND 15 (Lab Only):		
CENTRAL LAB	• Endocrine hormones: • Progesterone	

WEEK 16:

INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS Since Last Visit • MBQ	• PCOSQ • PGIA and PGIH
EXAM	• Weight and waist circumference • Vital signs • FG Score	• Pelvic ultrasound (TVU and TAU) • Urine pregnancy test • Acne lesion assessment and IGA

CENTRAL LAB	• Endocrine hormones:
	  • Fasting insulin
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
	• Elagolix single PK sample
	• Intensive PD sampling of LH, FSH
		• Clinical laboratory test (chemistry, hematology, lipid panel, urinalysis)
		• Liver transaminases (ALT, AST) and fractionated bilirubin

TREATMENT	• Dispense study drug	• Review subject dosing and perform drug reconciliation

NOTE: Site should remind subject 2 weeks prior to FG score to avoid use of all hair removal procedures and products.

WEEKS 17, 18, AND 19 (Lab Only):

CENTRAL LAB	• Endocrine hormones: • Progesterone

WEEK 20:		
INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS Since Last Visit	
EXAM	• Urine pregnancy test	

CENTRAL LAB	• Liver transaminases (ALT, AST) and fractionated bilirubin
	• Endocrine hormones:
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
		• Elagolix single PK sample
		• LH/FSH single PD sample

TREATMENT	• Dispense study drug	• Review subject dosing and perform drug reconciliation

WEEKS 21, 22, AND 23 (Lab Only):		
CENTRAL LAB	• Endocrine hormones: • Progesterone	

WEEK 24/
PREMATURE
DISCONTINUATION:

INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary • Review e-Diary entries
PRO	• C-SSRS Since Last Visit • MBQ	• PCOSQ • PGIA and PGIH
EXAM	• Physical exam • Weight and waist circumference • Vital signs • Gynecological (pelvic and breast) exam • Acne lesion assessment and IGA	• MRI if required • Pelvic ultrasound (TVU and TAU) • Urine pregnancy test • DXA scan • FG Score

CENTRAL LAB	• Endocrine hormones/test:
	  • Fasting insulin
	  • HbA1c
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
		• Clinical laboratory test (chemistry, hematology, lipid panel, urinalysis)
		• Liver transaminases (ALT, AST) and fractionated bilirubin
		• Elagolix single PK sample
		• LH/FSH single PD sample
		• Serum pregnancy test
		• Optional biomarker sample: whole blood (DNA and RNA), serum, plasma

TREATMENT	• Review subject dosing and perform drug reconciliation	

NOTE: If the Premature Discontinuation visit takes place at or before Week 12, a DXA scan would not be required.

UNSCHEDULED VISIT:

INTERVIEW	• AE assessment • Concomitant therapy • Birth control attestation	• Contraceptive counseling/dispense nonhormonal contraceptives as necessary
EXAM	• Weight and waist circumference • Vital signs	• Urine pregnancy test

CENTRAL LAB	• Endocrine hormones:
	  • Fasting insulin
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
		• Clinical laboratory test (chemistry, hematology, lipid panel, urinalysis)

2.3 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit.

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

30 DAYS POST-TREATMENT FOLLOW-UP:

INTERVIEW	• AE assessment • Concomitant therapy	

CENTRAL LAB	• Serum pregnancy test
	• Endocrine hormones:
	  • Fasting insulin
	  • Androstenedione
	  • AMH
	  • Testosterone/SHBG
	  • E2
	  • Progesterone
		• LH/FSH single PD sample

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.

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.

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the research. The written consent for biomarker research 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. A subject may withdraw consent for optional biomarker samples at any time and remain in the main study. Data generated from the optional biomarker samples before subject withdrawal of consent will remain part of the study results.

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

3.2 Medical History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at Washout (if applicable) or during the Screening Period for those subjects who do not require washout. The medical history will be reviewed and updated at Screening. The subject's medical history will be updated at the Baseline visit. This updated medical history will serve as the baseline for clinical assessment.

3.3 Gynecological/Obstetrical and PCOS History

A detailed gynecological/obstetrical and PCOS 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 PCOS, including year of diagnosis and PCOS 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 PCOS or other gynecological conditions
- Prior use of nonhormonal medications for the treatment of PCOS including pain medication, including dates of use for 12 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 PCOS history will be reviewed and should be updated if needed prior to dosing on Baseline (randomization) and will serve as the Baseline for clinical assessment.

3.4 Adverse Event Assessment

Please refer to Section 4.2.

3.5 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 2.2 and Section 2.3; 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 either electronically or on paper (which will then be entered into the electronic case report form [eCRF]), as applicable.

Site staff should review all subject-completed questionnaires for logic and completeness before the subject leaves the study site.

Subjects will complete the self-administered patient-reported outcome (PRO) instrument (when allowed per local regulatory guidelines). Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. The MBQ, PGIA/PGIH, PCOSQ, and C-SSRS may be administered by site staff via phone or video conference. In this situation, sites will read the PRO questions and response options to the subject, record the subject's responses on paper (source), and transcribe into the electronic data capture (EDC) system. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may share the questionnaire by video conference or send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded in the source along with who collected the information.

Electronic Daily Diary (e-Diary) for Uterine Bleeding

An electronic patient-reported outcomes device (e-Diary) will be provided to all subjects during Screening after informed consent is obtained. The e-Diary contains training information for the subject, but the site staff may also provide training on the required entries in the e-Diary. Subjects will also be instructed to complete the diary at approximately the same time every day throughout the study.

Site staff should review subject e-Diary data regularly throughout the entire study beginning at Screening to ensure subject completion. Subject noncompliance should be addressed by the site in a timely manner and subject retraining documented at the site. Subjects who fail Screening will be instructed to return the e-Diary device to the site. All subjects will be instructed to return the e-Diary device to the site at the last study visit or Premature Discontinuation visit.

Subjects will use the e-Diary to record assessments of uterine bleeding (Appendix A).

Menstrual Bleeding Questionnaire (MBQ)

The MBQ is a 20-item questionnaire to evaluate heavy menstrual bleeding. The higher the score the heavier the menstrual bleeding burden.

The MBQ should be completed prior to any discussion of AEs or any review of laboratory findings at all applicable visits (Activity Schedule, Protocol Appendix D).

The subject should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

Patient Global Impression for Acne and Hirsutism (PGIA and PGIH)

The Patient Global Impression of Acne (PGIA) and Patient Global Impression of Hirsutism (PGIH) will be measured using a 5-point scale and the scores will be used to assess the subject's opinion on how her symptoms have changed since starting medication. The PGIA and PHIH should be completed prior to any discussion of AEs or any review of laboratory findings at all applicable visits (Appendix B).

Polycystic Ovary Syndrome Questionnaire (PCOSQ)

This study will utilize the PCOSQ developed by Cronin et al.[1] The PCOSQ is a 26-item questionnaire broken up into 5 domains: emotions, body hair, weight, infertility problems, and menstrual problems. Responses are scored on a 7-point Likert scale, with low scores reflecting worse quality of life.

The PCOSQ should be completed prior to any discussion of AEs or any review of laboratory findings at all applicable visits (Activity Schedule, Protocol Appendix D).

The subject should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

FG Score

The FG score will be used to quantify hirsutism.[2] Sites will instruct the subject to refrain from any and all hair removal for at least 14 days prior to applicable visits. Laser hair removal is prohibited throughout the duration of the study. Each of the 9 body areas that is most sensitive to androgen is assigned a score from 0 (no hair) to 4 (frankly virile), and these are summed to provide a hormonal hirsutism score. "Focal" hirsutism (score 1 to 7) is a common normal variant, whereas generalized hirsutism (score of 8 or more) is abnormal in the general United States population. The FG Score assessment will be performed by the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the FG Score can be performed at the next on-site visit.

Acne Lesion Assessment

Acne severity will be measured by:

1). Acne lesion count: Investigators will count the number of non-inflammatory lesions (comedones) and number of inflammatory lesions (papules, pustules, and nodules) on the subject's face and sum the values for a total number.

2). Investigator's global assessment (IGA) scale. The IGA scale is as follows:

0 – Clear or normal skin (no evidence of acne)

1 – Almost clear skin (some non-inflammatory acne is present with some non-inflamed papules. Papules may be developing but are not yet pinkish-red in color)

2 – Some non-inflammatory acne can be found with a few pustules and/or papules. There are no cystic acne lesions yet.

3 – Non-inflammatory acne dominates the area and a few inflammatory lesions can be found. There may or may not be one small cystic acne lesion in the area.

4 – Non-inflammatory and inflammatory acne lesions are more visible. There may or may not be a few cystic acne lesions.

5 – Severe inflammatory acne dominates the area. Several numbers of comedones, pustules, papules, and cystic acne are also present.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the Acne Lesion Assessment and IGA can be performed at the next on-site visit.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS[3] is a systematically administered instrument developed to track suicidal AEs 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 during Screening and on Baseline. During the Treatment Period, site staff will administer the C-SSRS Since Last Visit questionnaire at the time points specified in Section 2.2 and Section 2.3. The C-SSRS administered at the Baseline Visit will serve as the Baseline for clinical assessment.

During Screening or at the Baseline visit, prior to randomization, any subject noted to have any suicide attempt ever or suicidal ideation with plan within the last year, either via answering "yes" to question 4 and/or question 5 to the suicidal ideation portion of the C-SSRS, or via clinical interview, is not eligible for randomization. If the subject expresses suicidal ideation on the C-SSRS or via clinical interview at any time during the study, the investigator should take appropriate action and then notify the AbbVie TA MD. Appropriate steps will be taken to protect the subject (including possible discontinuation from the study and referral for appropriate psychiatric care).

3.6 Pharmacokinetic Sampling

Sparse PK sampling (for sites that opt in to this activity): Serial blood samples for the elagolix assay will be collected before the morning dose (0 hour) and at 1 (± 5 minutes), 2 (± 15 minutes), 4 (± 15 minutes), and 6 hours (± 15 minutes) after dosing on Study Weeks 1 and 4 (if sites choose not to participate in the optional sparse PK sampling, a single blood sample will be collected anytime upon subject's arrival at the site on Study Weeks 1 and 4). "Intensive PK sampling" was changed in Protocol Version 3.0 to "sparse PK sampling." The labels and references to "Intensive PK" in the study supplies and laboratory kits remain unchanged.

Single PK sample (for all sites): In addition, a single blood sample will be collected anytime upon subject's arrival at the site as indicated in the Activity Schedule (Protocol Appendix D). The samples will be assayed for elagolix concentration and exposures of elagolix will be summarized.

Plasma concentrations of elagolix will be determined by the Bioanalysis Department at AbbVie using a validated method. Refer to the Laboratory Manual for sample collection and shipment instructions.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the sparse PK sampling or single PK sample can be collected at the next on-site visit.

3.7 Pharmacodynamic Sampling

Intensive PD sampling: Serial blood samples for LH and FSH assay will be collected at Baseline according to the following schedule: 0 hour, 0.5 (± 5 minutes), 1 (± 5 minutes), 1.5 (± 5 minutes), 2 (± 15 minutes), 2.5 (± 15 minutes), 3 (± 15 minutes), 3.5 (± 15 minutes), and 4 (± 15 minutes) hours. On Study Weeks 1, 4, and 16, serial blood samples will be collected before the morning dose (0 hour) and at 0.5 (± 5 minutes), 1 (± 5 minutes), 1.5 (± 5 minutes), 2 (± 15 minutes), 2.5 (± 15 minutes), 3 (± 15 minutes), 3.5 (± 15 minutes), and 4 (± 15 minutes) hours after dosing.

In addition, a single blood sample will be collected anytime upon subject's arrival at the site on Study Weeks 8, 12, 20, and 24. The samples will be assayed for LH and FSH concentrations, and exposures of both hormones will be summarized.

Serum concentrations of LH, FSH, and other relevant hormones and laboratory tests will be determined by AbbVie (or people or companies working with AbbVie). Refer to the Laboratory Manual for sample collection and shipment instructions.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the intensive PD sampling or single PD sample can be collected at the next on-site visit.

3.8 Biomarker Research Sampling

Optional biomarker samples for DNA and RNA isolation from whole blood, serum, and plasma will be collected from consenting subjects 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 optional 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 PCOS and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the optional biomarker samples can be collected at the next on-site visit.

3.9 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 at every visit as noted in the Activity Schedule (Protocol Appendix D) throughout study participation on the importance of pregnancy prevention and the use of appropriate and effective methods of contraception.

Subjects must agree to use 2 forms of nonhormonal contraception (dual contraception) as indicated in the protocol.

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 a 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.
    (1) 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.
    (2) Subjects should only use the pregnancy prevention materials provided by the sponsor.
    (3) 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.
    (4) The site will provide contraceptives and other supplies (e.g., lubricants) to subjects at the time points specified in Section 2, as necessary.
    (5) 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.
    (6) The subject will be asked to attest by signature at the time of consent, and subsequently in a stand-alone attestation form at study visits specified in the Activity Schedule (Protocol Appendix D) that allowable methods of contraception, as described during the pregnancy prevention counseling, are being practiced.
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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

3.10 12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be obtained during the Screening Period to confirm subject eligibility for the study unless the subject had one performed within 6 months of Screening and has documentation of the requirements. The principal investigator or designee at the study site will sign and date the ECGs, determine whether any findings outside the normal physiological variation are clinically significant (in consultation with a cardiologist if necessary), and document this on the ECG report. The original ECG tracing with the physician's assessment will be retained in the subject's records at the study site.

3.11 Height, Weight, and Waist Circumference

Height will be measured at Screening only. Waist circumference should be measured at the umbilicus at visits as specified in Section 2. Body weight will be measured at scheduled visits as specified in Section 2. The subject will wear lightweight clothing and no shoes during weighing. BMI will be calculated in EDC at the Screening visit.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, height, weight, and waist circumference can be collected at the next on-site visit.

3.12 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse, and temperature will be obtained at visits as specified in Section 2. Blood pressure should be measured after the subject has been sitting for at least 5 minutes.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, vital signs can be collected at the next on-site visit.

3.13 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2. The physical examination performed on Study Baseline will serve as the baseline physical examination for the entire study. Any clinically significant physical examination findings after the

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

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, physical examination can be performed at the next on-site visit.

3.14 Gynecological (Pelvic and Breast) Examination

A complete breast and pelvic examination 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, if the subject is unable to come on-site, the gynecological examinations can be performed at the next on-site visit.

3.15 Papanicolaou (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 6 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 visit, the pap 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.

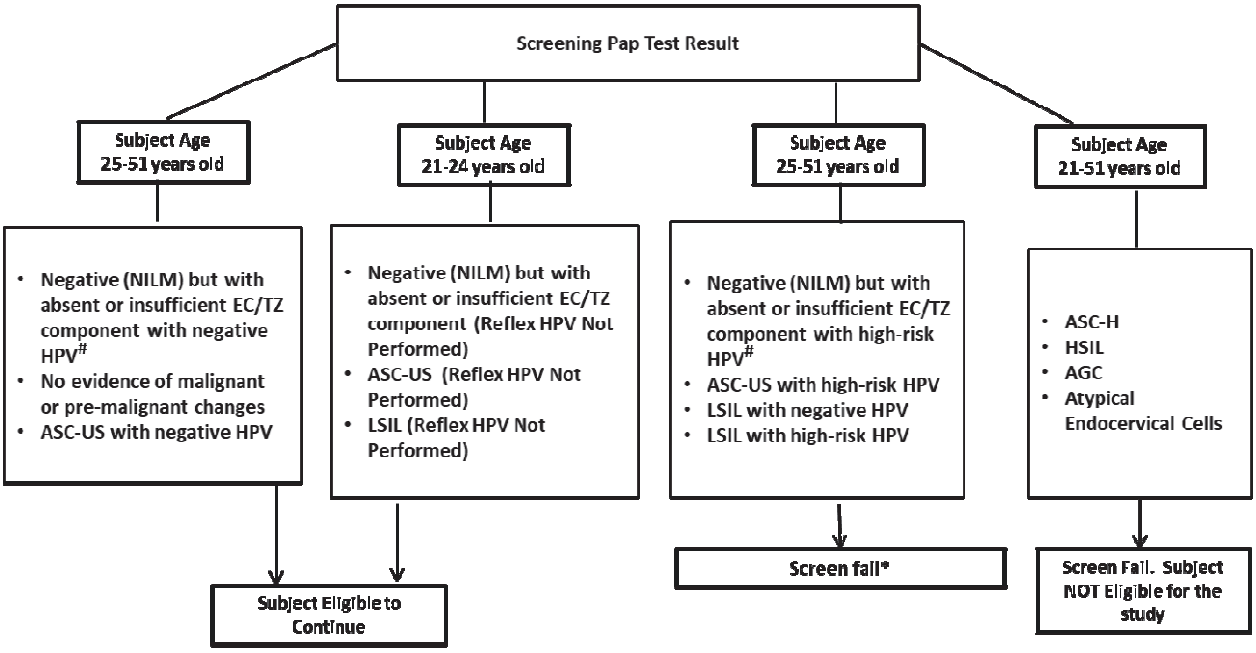
Subjects who are 25 to 35 years of age, with the Pap diagnosis of atypical squamous cells of undetermined significance (ASC-US), or low-grade squamous intraepithelial lesion (LSIL) and those > 30 years of age with negative intraepithelial lesion or malignancy (NILM) but absent or insufficient endocervical/transformational 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 colposcopy performed outside of the study, they may be rescreened if they have no other exclusionary criteria and 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.

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.

Note: Only subjects ≤ 35 years of age are being enrolled in this study.

3.16 Endometrial Biopsy

An endometrial biopsy will be performed in all subjects during the Screening Period unless one has been performed within 12 months of the Screening visit and original results available qualify subject to participate in the study or endometrial thickness < 5 mm on Screening TVU (see Protocol Section 5.1). Endometrial biopsy should show no clinically significant endometrial pathology. Subjects must have a confirmed 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.

Premedication for the endometrial biopsy procedure is allowable and should be recorded in source documents and on the appropriate eCRF. At the investigator's discretion, misoprostol for cervical dilatation is allowable. In addition, lidocaine may be used as local anesthesia on the cervix. Any medications used for the procedure should be recorded in source documents and on the appropriate eCRF. If there is a need for consideration for an office hysteroscopy to obtain the endometrial biopsy sample, the AbbVie TA MD (Section 1) should be consulted.

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

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 Baseline Visit. In case of an insufficient sample, the biopsy may be repeated; however, results must be available prior to Baseline. 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 per rescreening guidelines in the protocol.

3.17 Central/Local Imaging Procedures

Pelvic Ultrasound: TAU and TVU

The pelvic ultrasound (TAU and TVU) will be performed by the investigative site's or affiliated radiology department at the time points specified in Section 2. Images will be sent/transmitted to the central reader to determine subject eligibility for entry into the study and for subject evaluation during the course of the study.

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
- Presence of ovarian cysts (to include number, size [cm], location [right or left ovary], simple versus complex)
- Solid ovarian lesions > 1.5 cm longest diameter
- Persistent simple ovarian cyst > 5 cm in longest diameter
- Complex ovarian cyst > 3.5 cm in diameter at longest point
- An endometrioma > 3.5 cm in diameter (longest diameter)

A local reading will be performed to rule out pelvic masses or other significant pathologies. The investigator should consult the local ultrasound report (or images if the report is not available) in order to make any safety-related judgments concerning the subject. In this case, the local ultrasound reports will be maintained in the subject's source documents and copies may be collected upon request by the sponsor. Data from the local ultrasound report will not be reported in the eCRF unless associated with an adverse event.

Ovarian Findings

During Screening, if the initial pelvic ultrasound shows a simple ovarian cyst > 5 cm 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 Baseline Visit (randomization) and not meet exclusion criteria (i.e., persistent simple ovarian cyst > 5 cm). If the investigator notes endometrial thickness ≥ 5 mm, they may proceed to perform an endometrial biopsy based on the local read; however, the reading provided by the central reader should be used for entry into EDC.

In Screening, if any of the adnexal structures, such as an ovary, cannot be visualized on the pelvic ultrasound due to, for example, fibroid location and/or fibroid size, the subject may be eligible for randomization provided there are no exclusionary findings based on an alternate imaging that can evaluate that adnexa, such as a magnetic resonance imaging (per central reader request). The central reader may also request a magnetic resonance imaging scan at the Week 24/premature discontinuation visit, if needed. During the Screening Period, if the subject requires an MRI and the subsequent pelvic ultrasound is not readable, the subject will not continue to have pelvic ultrasounds. An MRI will be completed at the final visit.

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

Dual Energy X-ray Absorptiometry (DXA)

DXA scans of the lumber spine, femoral neck, and total hip will be performed at the time points specified in Section 2. Site training and qualifications, which include assessment of instruments, will be evaluated/approved by the central reader prior to screening of the first subject. Instructions on calibration and standardization of instruments and any additional required information will be specified in a manual from the central reader that will be provided to all study sites. Sites will need to obtain approval from the central reader prior to initiating study scans.

The screening DXA scan will be sent to the central reader to determine eligibility and serve as the baseline scan for subject management.

During the Treatment Periods, DXA scans will be performed for all subjects at Week 24 and will be submitted to the central reader for review and analysis. DXA scans will only be performed at the PD Visit if the subject has received study drug for at least 12 weeks.

DXA scans will be performed by qualified technologist/radiologists at the site or affiliated imaging facility using GE Lunar or Hologic equipment and per the acquisition guidelines provided by the Central Imaging Core Lab (central reader). The DXA technologist/radiologist or designee for each investigative site

should electronically submit the subject's DXA images to the central reader for review and analysis following acquisition. The central reader will be blinded to the subject's treatment assignment, but not to the corresponding time point.

Subject eligibility will be made based on the central reader review. Sites will receive reports from the central reader that detail the results (including Z-scores and bone mineral density (BMD) % change from Baseline, as applicable) of the DXA scans performed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

3.18 Dispense Study Drug

The site will dispense study drug at the time points specified in Section 2. The subject will take the first study drug dose the morning after the Baseline visit. Subjects will be instructed to self-administer their study drug throughout the Treatment Period.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Depending on the local regulations, provisioning of study drug for direct-to-patient (DTP) and direct-from-patient (DFP) transfer because of the COVID-19 pandemic will be available per request. AbbVie will submit any required notifications to the regulatory authority as applicable.

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

The investigator must discuss the DTP process with the subject:

- Obtain consent to provide delivery information to local courier and document this in the source.
- Obtain results of required safety procedures (e.g., urine pregnancy testing) before registering subject dispensation of study drug in IRT.
- Confirm that the subject will be available to accept delivery.
- The site will follow up with the subject after shipment is received.
- The subject should maintain the drug containers, as well as any unused drug for return to site.
- Sites will be required to retain documentation of the shipment for the IP accountability and monitoring. AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

Shipments may also include other study supplies (e.g., pregnancy tests, paper copies of PROs). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using a local courier selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature-controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due

to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

3.19 Clinical Laboratory Tests

The blood samples for serum chemistry tests will be collected following a minimum 8-hour fast prior to study drug intake. Subjects whose visits occur prior to the morning dose of study drug should be instructed to fast after midnight until the blood sample is collected in the morning and thereafter take their study drug with food. Subjects whose visits occur after the morning dose of study drug should be instructed to fast after breakfast until the study visit occurs. At the Baseline visit, a fasting blood sample should be collected. Blood samples should still be drawn if the subject did not fast for at least 8 hours. Fasting or nonfasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory and sent to the following certified laboratory addresses:

Covance CLS
8211 SciCor Drive
Indianapolis, IN 46214

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an AE.

Table 1. Clinical Laboratory Tests

Hematology	Clinical Chemistry (After Minimum 8-Hour Fast)	Lipid Panel (After Minimum 8-Hour Fast)
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)	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Serum creatinine Glucose Calcium Total protein Albumin Total bilirubin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Uric acid	Low-density lipoprotein cholesterol (LDL-C) High-density lipoprotein cholesterol (HDL-C) Triglycerides Total cholesterol **Endocrine Hormones/Tests** Follicle-stimulating hormone (FSH) Luteinizing hormone (LH) Fasting insulin Glycated hemoglobin (HbA1c) Testosterone Sex hormone binding globulin (SHBG) Progesterone Androstenedione Anti-Mullerian hormone (AMH) Estradiol (E2) Dehydroepiandrosterone sulfate (DHEAS) Reflexive thyroid-stimulating hormone Prolactin 17-OH-progesterone (17-OH-P)
Urinalysis	**Pregnancy Test**	**Other Tests (Screening Only)**
Specific gravity Ketones Leukocytes Nitrites Protein Blood Glucose pH	Serum pregnancy Urine pregnancy	Hepatitis B surface antigen (HBsAg) Hepatitis C virus antibody (HCVAb) Hepatitis C virus RNA (HCV RNA)
Additional Blood Samples to be Collected		
Elagolix single PK sample LH/FSH single PD sample Optional blood samples for exploratory research and validation studies.		

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects

to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be collected, the site will need to reach out to the medical monitor to determine further action and if study drug should be discontinued.

Laboratory samples indicated in Table 1 will be sent to the certified central lab selected for this study. All laboratory samples listed above will be assessed using a certified laboratory selected for this study and these data will be used for data analysis. The central laboratory will provide instructions regarding the collection (including any fasting requirements), processing, and shipping of samples. Blood draws should be performed after vital signs are conducted at a visit.

Clinical chemistry samples, insulin, and lipid panel 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.

The central laboratory will provide the laboratory results to the investigative site where the investigator will review, sign, and date them. For any value outside of the reference range, the investigator will review and indicate on the report if the result is clinically significant or not clinically significant. The investigator will evaluate clinically significant laboratory values per standard of care which may include repeating the test to verify the out-of-range value. Clinically significant laboratory abnormalities after randomization may be documented as AEs, depending on the investigator's interpretation.

All screening laboratory results must be reviewed prior to Baseline, including any repeated test results. Screening laboratory tests may be repeated one time prior to the Baseline Visit; however, results must satisfy entry criteria prior to randomization. Subjects should not be randomized at Baseline Visit if screening laboratory results do not meet entry criteria or the investigator assesses them as clinically significant. The most recent laboratory test results obtained prior to the Baseline Visit predose samples will serve as the Baseline for clinical assessment.

The investigator will receive sponsor-defined alerts from the central laboratory. The investigator will review the lab alerts and assess clinical significance for potential AEs.

Serology Testing for Hepatitis

The central laboratory will test all subjects for hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) during the Screening Period. HCV RNA testing will be performed for those subjects with a positive HCV Ab. A positive HBsAg or detectable HCV RNA will exclude subject from participation. Borderline hepatitis test results should be repeated.

Lipid Panel

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

obtained with less than 8 hours of fasting, the source documents and the lab requisition should be marked to indicate that the sample was obtained under nonfasting conditions.

Pregnancy Tests (Serum and Urine)

Urine and/or serum 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 Baseline must be reviewed and confirmed to be negative prior to randomization.

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 Baseline 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 site should instruct the subject to complete a Premature Discontinuation visit within 2 to 7 days of study drug discontinuation.

If a subject is confirmed as pregnant, the subject will be prematurely discontinued from the study drug. For any subject who has a positive serum pregnancy test result, a transvaginal ultrasound (TVU) must be conducted as early as possible in the first trimester in order to assess the gestational age and estimated due date.

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 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

Urinalysis

Urinalysis will be completed at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

3.20 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug 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 feels are 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.

4 SAFETY MANUAL

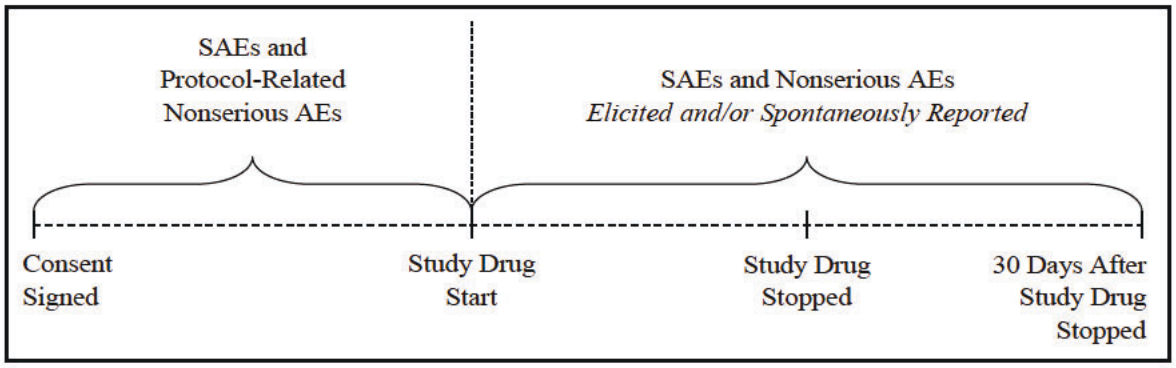
4.1 Methods and Timing of Safety Assessment

All serious adverse events (SAEs) as well as protocol-related nonserious AEs (e.g., occurrence during Screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days after discontinuation of study treatment, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the Post-Treatment Period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected).

Adverse events of special interest, such as elevated liver transaminases, decreased BMD/ bone fractures, and all mood- and depression-related events, will require additional information, to be collected in the EDC system.

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

Figure 2. Adverse Event Collection



AE = adverse event; SAE = serious adverse event

4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent AEs (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent AEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given

MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

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's being made aware of the SAE by entering the SAE data into the 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 non case report forms (CRFs) and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site's 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. AP31
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]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Office: [redacted]
Mobile:
Fax:

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

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. In the event of a positive urine pregnancy test, 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 site will follow the course of the subject's pregnancy and report to the sponsor on the health of the subject and fetus at each trimester, the outcome, the newborn at the first post-delivery pediatrician visit, and the infant 6 to 12 months post-delivery. 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.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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

COVID-19 infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and listed in Section 4.3. The following COVID-19 related supplemental eCRFs should be completed:

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

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed in Section 4.3 before reintroducing study drug.

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

The study drug (elagolix or matching placebo) will be dispensed in the form of capsules at the visits listed in Section 2.2.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that a subject cannot come to the site because of the COVID-19 pandemic, the site may contact the IRT for kit assignment after ensuring subject is eligible to continue with study drug dosing and confirming that a home urine pregnancy test was performed and the result was negative. Study drug dispensing can then be undertaken as outlined in Section 3.18.

6.2 Packaging and Labeling

All study drugs will be supplied in blister cards.

Each blister card will be labeled as required per country requirements.

The labels must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the

label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff before dispensing to subjects.

Storage and Disposition of Study Drug

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

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

6.3 Method of Assigning Subjects to Treatment Groups

This is a Phase 2, multicenter, randomized, double-blind (sponsor-unblinded), placebo-controlled study. All eligible subjects will receive elagolix or matching placebo.

At the screening visit, all subjects will be assigned a unique subject number through the use of the IRT. 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. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

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

6.4 Selection and Timing of Dose for Each Subject

Study drug will be administered at the scheduled visits (Section 2.2) for the randomized subjects. Subjects will be instructed to take study drugs at the same time every day.

Study drug will be provided by AbbVie as capsules in dosages of 25 mg, 75 mg, 150 mg, and placebo capsules.

Study drug will be taken orally as 3 capsules each day.

7 REFERENCES

1. Cronin G, Guyatt L, Griffith E, et al. Development of a health-related quality-of-life questionnaire (PCOSQ) for women with polycystic ovary syndrome (PCOS). J Clin Endocrin and Metab. 1998;83(6):1976-87.
2. Hatch R, Rosenfield RS, Kim MH, et al. Hirsutism: implications, etiology, and management. Am J Obstet Gynecol. 1981;140(7):815-30.
3. Columbia-Suicide Severity Rating Scale (C-SSRS) [homepage on the Internet]. Columbia University Medical Center [cited December 04, 2018]. Available from: http://cssrs.columbia.edu/.

APPENDIX A. E-DIARY FOR BLEEDING

Describe your uterine bleeding in the last 24 hours:

1. NONE
2. SPOTTING (a light amount of bleeding noted, no protection or panty shield only).
3. BLEEDING (1 or more tampons or pads required in last 24 hours).

eDiary for Bleeding -English-US-V1

APPENDIX B. PATIENT GLOBAL IMPRESSION FOR ACNE AND HIRSUTISM

Patient Global Impression for Acne (PGIA)

Please choose the response below that best describes the overall change in your acne since you started taking the study medication.

□ Much better

□ A little better

□ No change

□ A little worse

□ Much worse

Patient Global Impression for Hirsutism (PGIH)

Please choose the response below that best describes the overall change in your hair growth since you started taking the study medication.

□ Much better

□ A little better

□ No change

□ A little worse

□ Much worse