1.0 Title Page

Clinical Study Protocol M12-816

Extension Study to Evaluate the Efficacy and Safety of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

Incorporating Administrative Changes 1 and 2 and Amendment 1

AbbVie Investigational Product:	Elagolix (ABT-620)
Date:	18 December 2017
Development Phase:	3
Study Design:	Phase 3, double-blind, Extension Study evaluating the long-term efficacy and safety of elagolix administered alone and in combination with add-back therapy (estradiol/norethindrone acetate or E2/NETA) for the management of premenopausal women with HMB associated with uterine fibroids in subjects who participated in Study M12-815 or Study M12-817
Investigator(s):	Multicenter Trial: Investigator information is on file at AbbVie
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted] Medical Director AbbVie 1 North Waukegan Road North Chicago, IL 60064 Phone: Cell: Fax: [redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Confidential Information

No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	29 July 2016
Administrative Change 1	08 August 2016
Administrative Change 2	25 August 2016

The purpose of this Amendment is to:

- Update Table 1, Visit and Assessment Windows to remove MRI from Post-Treatment Follow Up Period Month 6

  Rationale: *MRI is not required at Post-Treatment Month 6*
- Update Section 5.1 Overall Study Design and Plan, Visit Windows to clarify Treatment Period Visit schedule.

  Rationale: *Clarify the scheduling of visits in the Treatment Period is based on the date of the Day 1 Visit.*
- Update Section 5.3.1.1 Study Procedures, Mammogram to clarify when a mammogram is performed at the Premature Discontinuation Visit.

  Rationale: *A mammogram is only required at the Premature Discontinuation Visit if it has been approximately 12 months since the Screening mammogram was performed.*
- Update Section 5.3.3.2 Secondary Efficacy Variable to remove fibroid and uterine volume.

  Rationale: *This is included in other efficacy variables.*
- Update Section 5.4 Removal of Subjects from Therapy or Assessment to clarify when in the Study, surgical interventions and elevated liver enzymes constitute study withdrawal.

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

- Update Appendix C Study Activities – Treatment Period and Post-Treatment Follow-Up Period footnote for mammogram at the Treatment Period Premature Discontinuation Visit

  Rationale: *To clarify when a mammogram is performed at the Treatment Period Premature Discontinuation Visit.*

- Update Section 5.3.1.1 Study Procedures, Endometrial Biopsy to remove the sixth paragraph

  Rationale: *Sixth paragraph is a repeat of the text in the second paragraph and is not required*

- Update Section 5.4.1 Discontinuation of Individual Subjects to clarify Post-Treatment Follow-Up Period Visit schedule for subjects who prematurely discontinue

  Rationale: *Clarify the scheduling of visits in the Post-Treatment Follow-Up Period is based on the date of the last dose of study drug for subjects who prematurely discontinue from study drug treatment.*

- Update Section 5.5.5 Blinding of Investigational Product to add time period AbbVie will remain blinded.

  Rationale: *To clarify the time period AbbVie will remain blinded.*

- Update Section 8.1.2 Data Sets Analyzed to change modified intent to treat (mITT) analysis to full analysis and remove requirement for at least one post baseline visit.

  Rationale: *To use consistent analysis set across efficacy analysis.*

- Update Section 8.1.7.1.1 Primary Analysis to change modified intent to treat (mITT) analysis to full analysis and remove requirement for at least one post baseline visit.

  Rationale: *To use consistent analysis set across efficacy analysis.*

- Update Section 8.1.7.1.2 Derivation of Primary Efficacy Endpoint to add evaluable to AH data reported.

  Rationale: *To clarify AH data used for primary endpoint.*

- Update Section 8.1.7.1.3 Multiple Imputation to remove last sentence and add method to summarize responders.

  Rationale: *To clarify how percentage of responders will be summarized.*

- Update Section 8.1.7.1.4 Sensitivity Analysis of the Primary Efficacy Variable to clarify the analysis data set used.

  Rationale: *To be remain consistent with the type of analysis.*
- Update to add Section 8.1.7.3 Other Efficacy Variables.

  Rationale: *To differentiate these variables from secondary variables.*
- Update Section 8.1.7.3.1 Reduction in Bleeding to remove the last sentence.

  Rationale: *To remain consistent with other efficacy variables.*
- Update Section 8.1.8.4 Bone Mineral Density percentage of subjects summarized.

  Rationale: *To clarify the percent change in BMD to be summarized for each treatment group.*
- Update Section 8.2, Determination of Sample Size to remove the first sentence

  Rationale: *This information is already specified in Section 5.2, Selection of Study Population.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M12-816
Name of Study Drug: Elagolix (ABT-620)	**Phase of Development:** 3
Name of Active Ingredient: Elagolix sodium	**Date of Protocol Synopsis:** 18 December 2017
Protocol Title: Extension Study to Evaluate the Efficacy and Safety of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids	
Objective: The objectives of this study are to evaluate the long-term efficacy and safety of elagolix administered alone and in combination with add-back therapy (estradiol/norethindrone acetate or E2/NETA) to reduce heavy menstrual bleeding (HMB) associated with uterine fibroids for up to 12 months (initial 6 months if on active treatment in the Pivotal Study M12-815 or Study M12-817 and an additional 6 months in this Extension Study). The study will also evaluate the effects of the treatment regimens on hypoestrogenic side effects, changes in bone mineral density (BMD) as assessed by Dual Energy X-Ray Absorptiometry (DXA), and vasomotor symptoms, such as hot flush.	
Investigators: Multicenter trial. Investigator information is on file at AbbVie.	
Study Sites: Approximately 250 sites	
Study Population: Subjects who completed the 6-month Treatment Period of their respective Pivotal Study, have signed informed consent and meet eligibility criteria will be eligible for participation into this Extension Study.	
Number of Subjects to be Enrolled: Approximately 400	
Methodology: This Extension Study is designed to: • Obtain 6 months of treatment data in subjects who were randomized to placebo in one of the two Pivotal Studies and subsequently randomized to receive 6 months of treatment with elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD. • Obtain 12 months of continuous treatment data in subjects who received elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD for 6 months in one of the two Pivotal Studies and will continue to receive an additional 6 months of the same treatment in this study. • Obtain data on endometrial health (TAU, TVU and endometrial biopsy). • Assess bone mineral density, bone health and general safety with long-term treatment and recovery during Treatment and Post-Treatment Follow-Up Period (up to 12-Months of Treatment and 12-Months of Post-Treatment Follow-Up).	

Methodology (Continued):

Following completion of the 6-Month Treatment Period, all subjects will then enter into a 12-Month (48 weeks) Post-Treatment Follow-Up Period. Approximately 400 subjects will be enrolled in this Extension Study. Among them, those subjects who received elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD in the Pivotal Studies will continue to receive the same treatment while subjects who received placebo in the Pivotal Studies will be randomized in a 1:1 ratio to one of the following two treatment groups:

- elagolix 300 mg BID
- elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD

Study Duration:

The total duration for this Extension Study is approximately 18 months.

The study consists of 2 periods:

1.) 6-Month Treatment Period; and

2.) 12-Month Post-Treatment Follow-Up Period.

Treatment Period:

- After providing informed consent and meeting eligibility criteria, subjects will enter a 6-Month (24 weeks) Treatment Period.
- Subjects who received placebo during the Pivotal Studies will be randomized in an equal ratio to receive either elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD during the Treatment Period.
- Subjects who received elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD during their respective Pivotal Studies will remain on the same treatment during the Treatment Period of this Extension Study.

During the Treatment Period, subjects will be required to return to the study site monthly. Study visits will occur at Day 1, and then monthly (28-day intervals) at Month 1 through Month 6. Additional study visits may occur either for subjects returning their sanitary products at a Product Collection Visit or for a Premature Discontinuation Visit.

At each monthly visit during the Treatment Period, except Treatment Month 6, a 1-Month supply of study drug will be dispensed, urine and/or serum pregnancy testing will be performed, and contraception counseling will occur. All subjects will self-administer study drug, elagolix 300 mg twice daily (once in the morning and once in the evening approximately 12 hours apart) and E2/NETA or matching Placebo once daily (in the morning) orally throughout the 6-Month Treatment Period.

Treatment Period (Continued):

Treatment Period Assessments:

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

A pelvic ultrasound will be performed in all subjects at Month 3, Month 6 or Premature Discontinuation Visit, if applicable, to assess volume of the largest fibroid, uterine volume, endometrial thickness and potential presence of ovarian and uterine pathology. During the Treatment Period, Magnetic Resonance Imaging (MRIs) in a subset of subjects will be conducted at Month 6 or Premature Discontinuation Visit, if applicable, to assess fibroid and uterine volume. An endometrial biopsy will be performed in all subjects at the Month 6 or at the Premature Discontinuation Visit (if the subject prematurely discontinues after the Month 3 Visit).

Subjects who enter the Extension Study with BMD decrease < 5% in both spine and total hip will require a DXA scan at Month 6. Subjects who enter the Extension Study with BMD decrease ≥ 5% in spine or total hip require a DXA scan at Month 3 of this Extension Study. If the Month 3 DXA scan shows BMD decrease < 8% in spine, total hip, and femoral neck, the subject can continue in the Extension Study with a DXA scan to be performed at Month 6. If, however, the Month 3 DXA scan shows BMD decrease ≥ 8% in spine, total hip, or femoral neck, the subject must discontinue treatment and enter the Post-Treatment Follow-Up Period.

Sites will continue to collect concomitant medications and assess for adverse events at every visit.

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

Pregnancy (urine and/or serum) tests will be performed at each visit throughout the study. Subjects will continue to be required to participate in contraceptive counseling, and at each visit will be reminded of the importance of using appropriate and effective forms of dual non-hormonal contraceptives to promote pregnancy prevention.

During the Treatment Period, blood samples will be collected to assay for serum estradiol and progesterone, and to measure plasma concentrations of elagolix and NETA, as well as blood samples for clinical safety labs, (including lipid panel) will be collected during the study.

Post-Treatment Follow-Up Period:

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

During the Phone Visits, Site Personnel will discuss adverse events, concomitant medications, if applicable, obtain the results of the subject's self-administered urine pregnancy test and will remind subjects of the importance of consistent use of appropriate and effective dual non-hormonal contraception through the Post-Treatment Follow-Up Period. Subjects may begin taking hormonal contraception or Tranexamic Acid (Lysteda, Cyklokapron, Cyclo-f) after completing the Post-Treatment Follow-Up Month 2 Visit and return to first full menses in the Post-Treatment Follow-Up Period.

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

During the On-Site Visits, procedures such as TAU, TVU, MRI (if applicable), DXA, clinical safety labs and pregnancy testing will be performed. At the Post-Treatment Follow-Up Period Month 12 Visit, procedures including vital signs, lipid panel, Apolipoprotein A and B and DXA will be performed.

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

Central Laboratory and Central Imaging Vendors:

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

Analysis of Menstrual Blood Loss:

This study will utilize the alkaline hematin (AH) method for measuring MBL volume. Alkaline hematin is an objective and reliable measurement of total MBL based on the quantitation of menstrual blood collected on sanitary products.

Key Criteria for Inclusion/Exclusion:

Key Inclusion Criteria:

1. Subject has voluntarily signed and dated the informed consent form (ICF), approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to initiation of any study-specific procedures.
2. Subject has completed the 6-Month Treatment Period of their respective Pivotal Study (either Study M12-815 or Study M12-817).
3. Subject has BMD decrease < 8% in the spine, total hip and femoral neck at Month 6 of the Treatment Period of their respective Pivotal Study.
4. Subject's urine and/or serum pregnancy test(s) results were consistently negative during the Treatment Period of their respective Pivotal Study and at Day 1 of this Extension Study.

Key Criteria for Inclusion/Exclusion (Continued):

Key Inclusion Criteria (Continued):

5. Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Treatment Period and Post-Treatment Follow-Up Periods. (Subject may start hormonal contraception after completion of the Post-Treatment Follow-Up Month 2 Visit and return to first full menses). Acceptable methods of dual contraception include the following combinations:
   - Condom with spermicide (foam, gel or polymer film)
   - Diaphragm with spermicide (condom may or may not be used)
   - Cervical cap with spermicide (condom may or may not be used)

   Subject is not required to use dual contraception methods if:
   - Sexual partner(s) is vasectomized, at least 6 months prior to Screening.
   - Subject practices total abstinence from sexual intercourse, as the preferred lifestyle of the subject; periodic abstinence is not acceptable.
   - Subject had a bilateral tubal occlusion (including ligation and blockage methods such as Essure®), at least 4 months prior to Screening.
   - Subject is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non hormonal contraception as noted above.
6. Subject's endometrial biopsy from the Month 6 Visit of their respective Pivotal Study shows no clinically significant endometrial pathology.

Rationale For Inclusion Criteria:

1	This is standard criterion in accordance with harmonized Good Clinical Practice (GCP)
2, 3	These criteria were selected to ensure an appropriate subject population of premenopausal women with HMB associated with uterine fibroids (prognostic and predictive)
4, 5	The impact of elagolix on pregnancies or breastfed infants is unknown and there is a possible risk of miscarriage due to changes in hormone levels; therefore, these criteria ensure pregnant women are not enrolled into the study and adequate precautions are taken to avoid pregnancy during study participation (prognostic and risk)
6	This is standard criteria to ensure general good health and the safety of the subjects (risk)

Key Criteria for Inclusion/Exclusion:

Key Exclusion Criteria:

1. Subject met criteria for removal from therapy in her respective Pivotal Study.
2. Subject is planning a pregnancy within the next 18 months.
3. Subject has current suicidal ideation as evidenced by answering 'yes' to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at Treatment Period Month 6 Visit of her respective Pivotal Study.

Key Criteria for Inclusion/Exclusion (Continued):

Key Exclusion Criteria (Continued):

4. Subject has a newly diagnosed clinically significant medical condition that requires intervention **OR** an unstable medical condition that makes the subject an unsuitable candidate for the study in the opinion of the Investigator (including, but not limited to: uncontrolled diabetes mellitus, uncontrolled hypertension, epilepsy requiring anti-epileptic medication, unstable angina, confirmed inflammatory bowel disease, hyperprolactinemia, clinically significant infection or injury or symptomatic endometriosis [confirmed by laparoscopy/laparotomy]).
5. Subject is using any systemic corticosteroids for over 14 days or is likely to require treatment with systemic corticosteroids during the course of the study. Over-the-counter and prescription topical, inhaled, intranasal or injectable (for occasional use) corticosteroids are allowed.
6. Subject, who in the judgment of the Investigator, will be unable or unwilling to comply with study-related assessments and procedures, including collection of sanitary products.

Rationale for Exclusion Criteria:

1, 3, 4, 5	This is standard criteria to ensure general good health and the safety of the subjects (risk)
2	The impact of elagolix on pregnancies or breastfed infants is unknown and there is a possible risk of miscarriage due to changes in hormone levels; therefore, these criteria ensure adequate precautions are taken to avoid pregnancy or breastfeeding while receiving elagolix (risk)
6	This criterion was added to ensure the population of subjects enrolled will comply with study-related procedures and subject collection requirements throughout the entire study (predictive)

Investigational Products:	Elagolix sodium 300 mg tablets Estradiol 1 mg/norethindrone acetate 0.5 mg (E2/NETA) capsules
Doses:	Elagolix 300 mg BID plus placebo for E2/NETA Elagolix 300 mg BID plus estradiol/norethindrone acetate (E2 1 mg/NETA 0.5 mg) QDElagolix 300 mg BID alone plus placebo for estradiol/norethindrone acetate (E2 1 mg/NETA 0.5 mg) QDElagolix 300 mg BID plus estradiol/norethindrone acetate (E2 1 mg/NETA 0.5 mg) QD Note: This study will evaluate an elagolix total daily dose of 600 mg, administered as 300 mg BID
Reference Therapy:	Placebo capsules to match E2/NETA for blinding
Mode of Administration:	Oral
Duration of Treatment: 6-Months	
Duration of Post-Treatment Follow-Up: 12-Months	

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint:

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

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

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

Secondary Efficacy Variables:

- MBL volume assessed using alkaline hematin methodology and UBQ
- Suppression of bleeding
- Hemoglobin concentration

Other Efficacy Variables:

- Amenorrhea
- Control of bleeding
- Bleeding days
- Fibroid and uterine volume
- UFS-QoL Questionnaire
- EuroQol (EQ-5D-5L) Questionnaire
- Health Care Resource Utilization (HCRU) Questionnaire
- Patient Global Impression of Change (PGIC) Questionnaires
- Work Productivity and Activity Impairment (WPAI) Questionnaire

Safety:

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

Statistical Methods:

Efficacy:

Separate summaries will be provided for each of the following groups of subjects:

1. Subjects randomized to elagolix 300 mg BID in the Pivotal Studies and continued to receive elagolix 300 mg BID in the Extension Study;
2. Subjects randomized to elagolix 300 mg BID plus E2/NETA QD in the Pivotal Studies and continued to receive elagolix 300 mg BID plus E2/NETA QD in the Extension Study;
3. Subjects randomized to placebo in the Pivotal Studies, and re-randomized to elagolix 300 mg BID in the Extension Study; and

Statistical Methods (Continued):

Efficacy (Continued):

4. Subjects randomized to placebo in the Pivotal Studies, and re-randomized to elagolix 300 mg BID plus E2/NETA QD in the Extension Study.

Unless otherwise specified, no statistical comparisons will be performed.

Primary Efficacy Analysis:

The primary analysis of the primary endpoint will be performed using the full analysis set, which is comprised of all subjects who took at least one dose of the study drug in this Extension Study.

The alkaline hematin method and the UBQ will be used to assess the MBL volume. The approach of handling missing data will be the same as in the Pivotal Studies.

The percentage of subjects with MBL volume < 80 mL at the Final Month and 50% or greater reduction in MBL volume from baseline to the Final Month in the Extension Study will be summarized by treatment group.

Analyses for Secondary and Other Efficacy Variables:

The change and percent change from baseline in MBL volume to each month and to the Final Month will be summarized for each treatment group. The percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline to each month in the Extension Study will be summarized by treatment group. The percentage of subjects with suppression of bleeding and the percentage of subjects with amenorrhea will be summarized by treatment group.

The change and percent change from baseline to the Month 6 in the Extension Study in hemoglobin concentration will be summarized by treatment group.

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

The change from baseline for Quality of Life assessments (e.g., UFS-QoL, EQ-5D-5L) will be summarized for each treatment group. For the PGIC-MB and PGIC-NBUFS, the number and percentage of subjects in each response category will be summarized by treatment group.

Safety:

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

Separate summaries will be provided for each of the following groups of subjects:

1. Subjects randomized to elagolix 300 mg BID in the Pivotal Studies and continued to receive elagolix 300 mg BID in the Extension Study;
2. Subjects randomized to elagolix 300 mg BID plus E2/NETA QD in the Pivotal Studies and continued to receive elagolix 300 mg BID plus E2/NETA QD in the Extension Study;
3. Subjects randomized to placebo in the Pivotal Studies, and re-randomized to elagolix 300 mg BID in the Extension Study; and
4. Subjects randomized to placebo in the Pivotal Studies, and re-randomized to elagolix 300 mg BID plus E2/NETA QD in the Extension Study.

Unless otherwise specified, no statistical comparisons will be performed.

The number and percentage of subjects having adverse events will be tabulated by primary System Organ Class (SOC) and MedDRA Preferred Term with a breakdown by treatment group. Hematology, chemistry, urinalysis, lipid panel, vital signs and endometrial biopsy variables will be summarized.

Statistical Methods (Continued):

Safety (Continued):

The within-group percent change from baseline to Month 6 in the Extension Study in BMD will be summarized by treatment group.

For subjects who have at least 12 months of total exposure to elagolix, the percent change from Baseline to Month 6 in the Extension Study in BMD will be compared between elagolix dose groups (elagolix 300 mg BID versus elagolix 300 mg BID plus E2/NETA QD) using analysis of covariance (ANCOVA) with treatment as the main effect and baseline BMD as a covariate. A two-sided 95% confidence interval will be constructed for the between-group difference in percent change from baseline to Month 6 in the Extension Study in BMD.

Sample Size:

All subjects who complete either the Pivotal Study M12-815 or Study M12-817, sign an inform consent form, and meet the inclusion/exclusion criterion will be eligible to enroll in this Extension Study. The two Pivotal Studies M12-815 and M12-817 have a planned enrollment of a total of 800 subjects. Based on assumptions related to discontinuation in the Pivotal Study and the estimated roll over rate into this Extension Study, approximately 400 subjects are expected to be enrolled in this Extension Study.

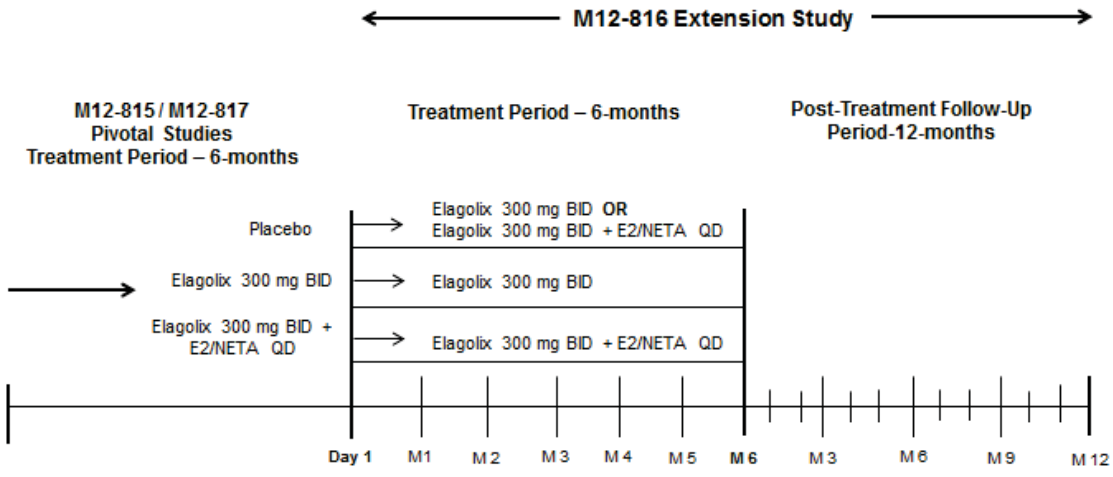
Pharmacokinetics/Pharmacodynamics:

Plasma concentrations of elagolix and norethindrone will be listed for each subject by visit day and dose regimen. Pharmacokinetic data may be combined with data from other studies in women.

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

Exposure-response analyses may be conducted as appropriate.

Study Schematic:



1.3 List of Abbreviations and Definition of Terms

Abbreviations

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

HCRU	Health Care Resource Utilization
HCV Ab	Hepatitis C Virus Antibody
Hgb	Hemoglobin
HIFU	High Intensity Focused Ultrasound
HMB	Heavy Menstrual Bleeding
HSIL	High-Grade Squamous Intraepithelial Lesion
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICL	Imaging Core Lab
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IR	Immediate Release
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra-Uterine Device
K_2EDTA	K_2-ethylenediaminetetraacetic acid
LDL	Low-density Lipoprotein
LH	Luteinizing Hormone
LNG-IUS	Levonorgestrel Intrauterine System
LSIL	Low-grade squamous intraepithelial lesion
M	Month (visit)
MAD	Multiple Ascending Dose
MBL	Menstrual Blood Loss
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Cell volume of RBC
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NETA	Norethindrone acetate
NBI	Neurocrine Biosciences Inc
P	Progesterone
Pap	Papanicolau
PCV	Product Collection Visit
PD	Premature Discontinuation

PGIC-MB	Patient Global Impression of Change – Menstrual Bleeding
PGIC-NBUFS	Patient Global Impression of Change – Non-Bleeding Uterine Fibroid Symptoms
PID	Pelvic Inflammatory Disease
P-gp	P-glycoprotein
PK	Pharmacokinetic
POC	Proof-of-Concept
PRO	Patient Reported Outcome
PTSD	Post-Traumatic Stress Disorder
QD	Once a day (quaque die)
QoL	Quality of Life
RANKL	Receptor activator of nuclear factor-κB ligand
RBC	Red Blood Cell
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT/ASAT	Serum glutamic-oxaloacetic transaminase/aspartate aminotransferase
SIS	Saline Infusion Sonohysterography
SGPT/ALAT	Serum glutamic-pyruvic transaminase/alanine aminotransferase
SPRM	Selective Progesterone Receptor Modulator
TA MD	Therapeutic Area Medical Director
T-SG	Trial-Specific Guidelines
TAU	Transabdominal Ultrasound
TDD	Total Daily Dose
TBG	Thyroxine-Binding Globulin
TSH	Thyroid Stimulating Hormone
TEAEs	Treatment-emergent adverse events
TVU	Transvaginal Ultrasound
UBQ	Uterine Bleeding Questionnaire
UFS-QoL	Uterine Fibroid Symptom Quality of Life Questionnaire
WBC	White Blood Cells
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

Pharmacokinetic and Statistical Abbreviations

ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
C_{max}	Maximum concentration in plasma
PD	Pharmacodynamic
PK	Pharmacokinetic
T_{max}	Time to maximum observed plasma concentration

Definition of Terms

Pivotal Study	Studies M12-815/M12-817: A Phase 3 Study to Evaluate the Efficacy and Safety of Elagolix in Combination with Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated with Uterine Fibroids in Premenopausal Women.
Extension Study	Study M12-816: Extension Study to Evaluate the Efficacy and Safety of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids.
Day 1 or Treatment Period Day 1	The day a subject takes her first dose of study drug in this Extension Study M12-816. The Day 1 Visit will occur only after completing Treatment Period of the Pivotal Studies M12-815/M12-817.
Monthly Visits: Treatment Period Months 1 through 6 and Post-Treatment Period Months 1 through 12	A month is defined as 28 days.
Product Collection Visits	Visits at which subjects return used sanitary products for assessment of alkaline hematin levels (either during Screening or the Treatment Period); visits should occur within approximately 5 days after the last sanitary product was collected during a bleeding and/or spotting episode.
Home Product Collection Visits	Product Collection Visit conducted at home by a Home Health Care Agent who will go to the subject's home to draw a venous blood sample and retrieve the collection keg to return to the study site.
Heavy Menstrual Bleeding	Menorrhagia or > 80 mL blood loss.
Vasomotor Symptoms	Examples: hot flush and night sweats.

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3.0 Introduction

3.1 Uterine Fibroids

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

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

Although often asymptomatic, fibroids may cause symptoms severe enough to warrant therapy in 20% to 50% of women[3] and the most common symptom is heavy or prolonged menstrual bleeding. Other symptoms may include anemia, pelvic pressure and pelvic organ compression, back pain, and adverse reproductive outcomes. Heavy menstrual bleeding (HMB) (menorrhagia, defined as > 80 mL per menstrual cycle)[1] is extremely inconvenient, can significantly impact quality of life and may lead to iron-deficiency anemia.

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

symptomatic uterine fibroids. Treatment with GnRH agonists such as Lupron® is effective but induces full gonadal suppression and menopause-like symptoms that limit their use to 3 months of presurgical treatment. High-dose progestins, oral contraceptives and tranexamic acid (Lysteda®-an antifibrinolytic drug) are used for short-term management of heavy uterine bleeding only. Recently, the selective progesterone receptor modulator (SPRM), ulipristal acetate, has been approved in the EU as a short-term preoperative treatment, as well as an extended intermittent treatment of women with of symptomatic uterine fibroids.

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

3.2 Elagolix

Elagolix is an orally active, non-peptide (GnRH) antagonist that is being developed by AbbVie for the management of endometriosis-related pain and the chronic management of HMB associated with symptomatic uterine fibroids. The initial preclinical and clinical evaluation of elagolix was conducted by Neurocrine Biosciences Inc. (NBI). Safety results from these studies show that elagolix is generally well tolerated. Elagolix, unlike injectable GnRH analogs, produces a dose dependent suppression of pituitary and ovarian hormones in women, i.e., from partial ovarian suppression at lower doses to full suppression at higher doses. A detailed discussion of the preclinical toxicology, metabolism, pharmacology and pharmacokinetics of elagolix in humans and a summary of clinical studies can be found in the Investigator's Brochure and is also discussed in lesser detail in Section 3.2.1 and Section 3.2.2.[7]

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

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

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

3.2.1 Preclinical Experience

3.2.1.1 Toxicology

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

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

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

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

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

3.2.2 Clinical Experience

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

Clinical Program Overview

As of 31 January 2016, a total of 3,417 subjects have received at least 1 dose of elagolix in clinical studies conducted by NBI and AbbVie (30 Phase 1 studies, 6 Phase 2 endometriosis studies, 2 Phase 2 uterine fibroid studies [Studies M12-663 and M12-813], and 1 ongoing Phase 3 endometriosis extension study [Study M12-665] and 2 ongoing Phase 3 endometriosis extension studies [Studies M12-667 and M12-821]). More than 1,000 of these subjects were dosed for ≥ 6 weeks. Of the 3,417 subjects, 95 were healthy men, 795 were healthy women, 1,296 were women with endometriosis, 221 were women with uterine fibroids, 16 were women with hepatic impairment, and 9 were women with

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

Twelve Phase 1 clinical studies (7 in healthy men and 5 in healthy women) and 6 Phase 2 studies (in women with endometriosis) were completed by NBI. To date, 18 Phase 1 studies have been completed by AbbVie. The Phase 3 endometriosis registration program consists of 2 replicate 6-month Pivotal Studies, Study M12-665 and Study M12-671 and 2 extension studies, Study M12-667 and Study M12-821, respectively. In women with HMB associated with uterine fibroids, 2 Phase 2 studies have been completed by AbbVie, Study M12-663 and Study M12-813. The Phase 3 uterine fibroid registration program consists of 2 Pivotal Studies, Study M12-815 and Study M12-817, and a single planned associated 6-month safety/efficacy extension study, Study M12-816.

Clinical Pharmacokinetic and Pharmacodynamic Summary

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

- Elagolix exposure (area under the plasma concentration versus time curve [AUC] and maximum concentration in plasma [C_{max}]) appears to be approximately dose-proportional across the daily dose range studied (25 to 400 mg). At single daily doses of 600 mg and above, more than dose proportional increases in elagolix exposures were observed.
- Elagolix displays biphasic disposition with a terminal elimination half-life of approximately 4 – 6 hours. Little or no accumulation resulted from BID (400 mg BID), or once daily (QD) (400 mg QD) dosing at steady state which is not deemed clinically relevant.
- Food decreases the AUC of the immediate-release tablet formulation by approximately 25%.

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

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

Effects on Ovulation

Elagolix is not a contraceptive and data on ovulation rates from the 3-month folliculogenesis study, Study M12-673, showed that the 100 mg BID, 150 mg QD, and 200 mg QD doses do not appear to differentiate. The percentage of subjects with at least 1 ovulation during the 3 months of elagolix treatment was 47.4% to 57.1%, and the percentage of subjects with ovulation was 28.1% to 33.3% within each month (28-day period). In contrast, when ovulation rates are counted by subject or by month, the 200 mg BID dose appears to decrease ovulation rates to almost half of that observed with the 150 mg QD dose. The 300 mg BID dose appeared to have a slightly lower ovulation rate than 200 mg BID (27% versus 32%), and when the standard-dose estradiol 1 mg/norethindrone acetate 0.5 mg (standard-dose E2/NETA) was co-administered with elagolix 300 mg BID, the ovulation rate decreased further to approximately 10%.

Summary of Safety Findings

Adverse Events Across Elagolix Studies

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

Adverse Events in Phase 2 Studies in Uterine Fibroids

Study M12-663

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

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

Study M12-813

Preliminary data from the completed Phase 2b study, Study M12-813, show that, overall, the percentage of subjects who reported treatment-emergent adverse events was generally similar across all treatment groups in both cohorts, ranging from 67.9% to 87.0%, with the highest values in the elagolix alone groups (300 mg BID, 80.0%; 600 mg QD, 87.0%).

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

Adverse Events of Special Interest

Adverse events of special interest in elagolix clinical studies include mood changing disorders (suicidality and depression), cutaneous adverse events, hot flush, ovarian-related events, BMD decrease and fractures, uterine bleeding and changes in serum lipids. In the completed Phase 2 studies in uterine fibroids, there was a higher percentage of women experiencing cutaneous/hypersensitivity events and hot flush with elagolix treatment compared with placebo. Adverse events of special interest are monitored continuously in all clinical studies.

Serious Adverse Events

As of 31 January 2016, 129 serious adverse events have been reported by 92/3,417 (2.7%) subjects who received elagolix. Serious adverse events in all completed studies and in ongoing Studies M12-667 and M12-821 through the data cutoff date of 31 January 2016 are captured in the analysis for this update. The most common serious adverse event was pelvic pain occurring in 8 subjects (0.2%) followed by induced abortion occurring in 4 subjects (0.2%) and spontaneous abortion and endometriosis, each occurring in 5 subjects (0.1%), and abdominal pain and uterine leiomyoma, each occurring in 4 subjects (0.1%). Among women participating in elagolix clinical trials, one subject delivered an infant with congenital pneumonia. During the Phase 2 clinical development

program in endometriosis, there were 2 pregnancy-related serious adverse events (congenital malformations, i.e., 1 cleft palate and 1 tracheoesophageal fistula), which occurred during treatment and were assessed as unrelated to elagolix.

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

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

Effects of Elagolix on Bone Mineral Density (BMD)

The effects of elagolix 300 mg BID alone and in combination with low-dose and standard dose E2/NETA were evaluated in the 6-month Phase 2b study (Study M12-813). BMD was assessed at the lumbar spine (L1-L4), femoral neck, and total hip via DXA at Screening and at Month 6 of the Treatment Period, or Premature Discontinuation.

Preliminary results from the 6-month Phase 2b uterine fibroid study, Study M12-813, demonstrate that treatment with elagolix 300 mg BID and 600 mg QD, significantly decrease BMD, which is partially mitigated by addition of E2/NETA in a dose-dependent manner. In Cohort 1, the mean percentage change from Baseline to Month 6 in BMD in the lumbar spine for the elagolix 300 mg BID alone group was –3.8% at Month 6; 19% of subjects had a 3 to $\leq$ 5% BMD decrease, 25% had > 5% to < 8% BMD decrease, and 8% had a $\geq$ 8% BMD decrease.

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

Effects of Elagolix on Clinical Laboratory Parameters

Data from the Phase 2 studies with elagolix in women with uterine fibroids showed dose-dependent increases in serum lipid parameters, corresponding to the degree of estrogen suppression and similar to those seen with other GnRH analogs. Changes in serum lipids, in particular total cholesterol and low-density lipoprotein cholesterol (LDL-C), were observed in this study, similar to those observed in postmenopausal women[8] and these changes, as expected, were somewhat attenuated by E2/NETA in a dose-dependent manner. Mean percentage increases from Baseline in total cholesterol, high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglycerides were observed across each of the elagolix treatment groups over the 6-month treatment duration. Ongoing clinical trials with elagolix suggest similar findings, again which are consistent with those noted with other GnRH analogs. While the significance of these lipid changes in premenopausal women with low-risk baseline lipid values is unknown, further monitoring and evaluation is needed. In all these studies, the increased lipid values usually occur during the first 1 to 2 months of elagolix use, stabilize or plateau, and return to pretreatment baseline levels within 1 to 3 months after elagolix is discontinued.

Uterine Bleeding in Phase 2 Studies in Uterine Fibroids

Studies with elagolix have shown that overall, patients on elagolix experienced fewer days of bleeding per month, reduced bleeding intensity, and extended intervals between bleeding episodes compared with patients on placebo. Some subjects experienced periods

of oligomenorrhea or amenorrhea with evidence of irregular bleeding as well, in particular at lower doses. The effect of elagolix on bleeding appeared to be dose-dependent.

Study M12-813

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

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

Endometrial Safety in Phase 2 Studies in Uterine Fibroids

Study M12-813

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

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

3.2.2.1 Pregnancy in Elagolix Studies

Pregnancies Outcomes (Across the Entire Elagolix Clinical Development Program)

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

As of 05 February 2016, 172 pregnancies have been reported among women participating in elagolix clinical trials, including 104 that occurred off-treatment (58 during Screening and 46 during Post-Treatment [had a conception date more than 30 days after the last dose of study drug]) and 68 On-Treatment (i.e., had conception date during the Treatment Period with study drug or were deemed to have a conception date within 30 days after the last dose of study drug). Among the 68 on-treatment pregnancies, 21 subjects had no exposure to elagolix (20 subjects treated with placebo only and 1 subject treated with oral contraceptives only). The remaining 47 on-treatment pregnancies were in elagolix-treated subjects, and 21were carried to term, with 18 subjects delivering live infants without complications (1 pair of twins). One subject delivered an infant with meconium aspiration pneumonia (MedDRA preferred term = congenital pneumonia). Two subjects who received 150 mg elagolix QD in Phase 2 endometriosis studies delivered infants with congenital anomalies: 1 infant with tracheoesophageal fistula with findings of patent ductus arteriosus, tricuspid valve incompetence, and pneumothorax and 1 infant with cleft soft palate. Internal and external causality assessment of these malformations supported that both congenital malformation cases were unlikely to be related to elagolix. In Phase 3 studies in endometriosis, 14 pregnancies have been reported in Study M12-665 and 6 have been reported in Study M12-671. In the aforementioned Phase 2b UF study, 1 on-treatment pregnancy has been reported.

Extensive counseling on pregnancy prevention along with a requirement for dual non-hormonal barrier contraception is utilized in all ongoing and planned elagolix clinical

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

Pregnancies must be reported immediately and study drug discontinued. Information on the outcome of the pregnancy will be collected. For live infant births, information on the health of the infant will be collected 6 to 12 months after delivery.

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

Efficacy in Phase 2 Uterine Fibroid Studies

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

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

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

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

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

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

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

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

- Robust efficacy in controlling HMB (composite bleeding endpoint of 91.9%, 85.5%, and 79% in the elagolix 300 mg BID alone, elagolix 300 mg BID plus low-dose E2/NETA, and elagolix 300 mg BID plus standard-dose E2/NETA treatment groups, respectively) associated with uterine fibroids
- Clinically meaningful improvement in quality of life measures and symptom severity scores as assessed by UFS-QOL
- Mitigation of BMD loss at the lumbar spine, with standard-dose E2/NETA
- Substantial dose-dependent reduction in the incidence of vasomotor symptoms, e.g., hot flushes
- No evidence of endometrial safety concerns
- Overall safety profile remains unchanged, with no new or unexpected findings to date.

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

Preliminary results from Study M12-813 show that all treatment arms (both doses of elagolix [300 mg BID and 600 mg QD] alone or in combination with either strength of E2/NETA) met the primary endpoint, which is the proportion of subjects who achieved an MBL volume of < 80 mL at the Final Month **and** 50% or greater reduction in MBL volume from Baseline to the Final Month compared to that of placebo (all $P < 0.001$), as measured by the alkaline hematin method.

AbbVie Ongoing Phase 3 Clinical Studies

Endometriosis

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

Phase 3 Clinical Development Program for Uterine Fibroids

The overall objective of the registration clinical development program is to generate requisite safety, tolerability, and efficacy data in 2 replicate 6-month Phase 3 Pivotal Studies, Studies M12-815 and M12-817, and 1 safety and efficacy Extension Study, Study M12-816 (to receive up to a total of 12 months of treatment) to support use of elagolix 300 mg BID with E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) for the intended indication of the chronic management of HMB associated with uterine fibroids.

Subjects in this Extension Study will have completed the 6-month Treatment Period in one of the Pivotal Studies (Studies M12-815 or M12-817). In this study, they will receive 6 months of therapy, for a total of up to 12 months of active treatment for those randomized in the Pivotal Studies to active treatment and a total of 6 months of treatment for those randomized to placebo in the Pivotal Studies.

The primary objective of the Pivotal Studies is to evaluate the efficacy and safety of elagolix 300 mg BID in combination with add-back therapy (E2/NETA) as compared to placebo to reduce HMB associated with uterine fibroids. The goal of the Extension Study is to generate data that supports long-term use of elagolix 300 mg BID in combination with E2/NETA.

Given the difficulties with extending placebo for periods beyond 6 months, the elagolix 300 mg BID alone arm serves as a reference arm in this Extension Study, which will be useful in fully understanding the protective effects of standard dose E2/NETA on BMD over a 12-month treatment period, therefore the primary objectives of this Extension Study are to:

- Evaluate the long-term efficacy and safety of elagolix administered alone and in combination with E2/NETA
- Reduce heavy menstrual bleeding (HMB) associated with uterine fibroids for up to 12 months (initial 6 months if on active treatment in the Pivotal Study M12-815 or Study M12-817 and an additional 6 months in this Extension Study), and
- Further characterize the impact of E2/NETA on the safety and tolerability (including bone mineral density and other hypoestrogenic effects and efficacy of elagolix.

3.3 Estradiol/Norethindrone Acetate

E2/NETA (1 mg E2 and 0.5 mg NETA) is a continuous combined oral estrogen/progestin regimen. E2/NETA is approved in the United States as postmenopausal hormone replacement therapy for the treatment of moderate to severe vasomotor symptoms

associated with menopause and the prevention of postmenopausal osteoporosis. E2/NETA is also approved in the United States for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause.

3.4 Differences Statement

Phase 2 studies in women with HMB associated with uterine fibroids demonstrated that elagolix 300 mg BID provides the most robust efficacy in reducing HMB, and E2/NETA is the optimal regimen for managing and limiting BMD loss, such that longer-term dosing is feasible.

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

3.5 Benefits and Risks

The most common symptom in premenopausal women with uterine fibroids is heavy menstrual bleeding (HMB). A safe and effective chronic pharmacologic therapy for symptomatic uterine fibroids, as an alternative to hysterectomy or other surgical intervention, has not yet been approved, which is the objective of the Elagolix Phase 3 Clinical Development Program. Results from Phase 2 studies in women with HMB associated with uterine fibroids demonstrated that treatment with elagolix 300 mg BID alone and in combination with E2/NETA provided robust efficacy in reducing HMB associated with uterine fibroids. Importantly, when co-administered with elagolix 300 mg BID, E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD mitigated BMD loss observed with elagolix 300 mg BID alone and substantially other hypoestrogenic adverse events such as hot flushes. Also co-administration of elagolix and E2/NETA attenuated increases in serum lipid parameters observed with elagolix 300 mg BID alone. Furthermore, there was no evidence of endometrial safety concerns and the overall safety profile remained unchanged, with no new or unexpected findings to date.

This therapeutic approach, if successful, could provide an alternative to surgical interventions, and/or semi-invasive procedures as a chronic pharmacologic treatment for HMB associated with uterine fibroids. Based on the totality of data to date from the Phase 2 clinical development program, the overall benefit/risk profile of elagolix 300 mg BID with E2/NETA appears to be favorable for the chronic management of HMB associated with uterine fibroids, and will be further defined in this Phase 3 trial.

4.0 Study Objective

The primary objective of this study is to evaluate the long-term efficacy and safety of elagolix administered alone and in combination with add-back therapy (estradiol/norethindrone acetate or E2/NETA) to reduce heavy menstrual bleeding (HMB) associated with uterine fibroids for up to 12 months (initial 6 months if on active treatment in the Pivotal Study M12-815 or Study M12-817 and an additional 6 months in this Extension Study).

The study will also evaluate the effects of the treatment regimens on hypoestrogenic side effects, changes in bone mineral density (BMD) as assessed by Dual Energy X-Ray Absorptiometry (DXA), and vasomotor symptoms, such as hot flush.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, double-blind, multicenter, Extension Study designed to:

- Obtain 6 month treatment data in subjects who were randomized to placebo in one of the two Pivotal Studies and subsequently randomized to receive 6 months of treatment with elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD in this study.
- Obtain 12 months of continuous treatment data in subjects who received elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD for 6 months in one of the two Pivotal

Studies and will continue to receive an additional 6 months of the same treatment in this study.

- Obtain data on endometrial health (TAU, TVU and endometrial biopsy).
- Assess bone mineral density, bone health and general safety with long-term treatment and recovery during Treatment and Post-Treatment Follow-Up Period (up to 12 months of Treatment and 12 months Post-Treatment Follow-Up).

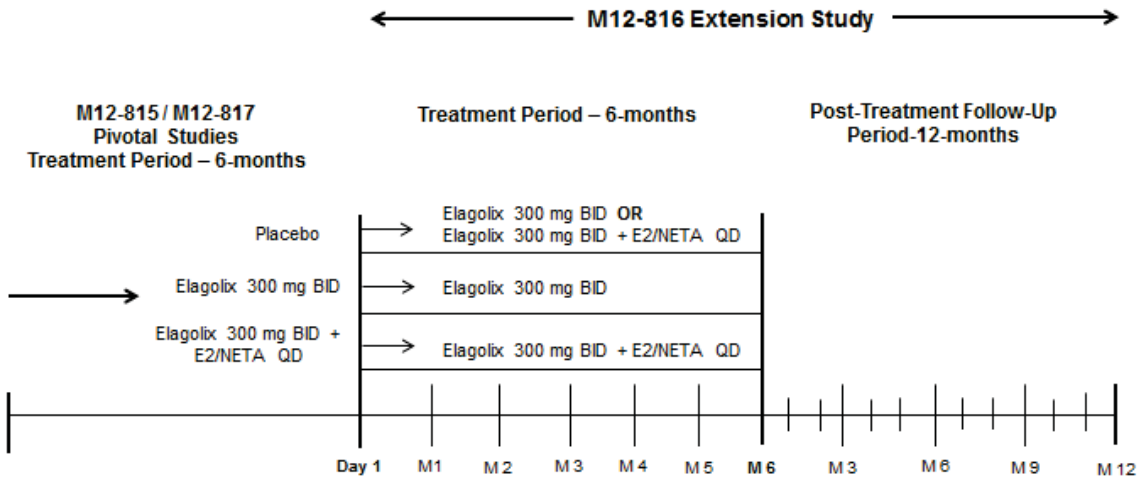
All subjects who completed the 6-Month Treatment Period in their respective Pivotal Study, who meet eligibility criteria and provide informed consent, will be eligible to enroll in this Extension Study. This study is designed to enroll approximately 400 subjects across approximately 250 clinical study sites to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations.

The study consists of 2 periods as follows:

1. 6-Month Treatment Period
2. 12-Month Post-Treatment Follow-Up Period

Following the 6-Month Treatment Period, subjects will enter into a 12-Month Post-Treatment Follow-Up Period. The Study Periods are illustrated in Figure 1.

Figure 1. Study Schematic



Treatment Period

Subjects will perform Day 1 Visit procedures after completing the 6-Month Treatment Period of their respective Pivotal Study. Subjects who do not meet criteria for inclusion into or are not willing to participate in the Extension Study will enter the Post-Treatment Follow-Up Period in their respective Pivotal Study, Study M12-815 or Study M12-817.

Subjects will continue to be assigned study drug kits via the IRT system for the Extension Study, after eligibility is confirmed and consent is obtained. Subjects who received active treatment in the Pivotal Study will continue to receive the same treatment; subjects randomized to placebo will be re-randomized in IRT to receive either elagolix 300 mg BID) or elagolix 300 mg BID plus E2/NETA QD for 6 months. Subjects will remain blinded to their original treatment received in the Pivotal Studies as well as their treatment in this Extension Study. The first dose of study drug will be administered at the study site on Day 1. Subjects will continue to self-administer study drug twice daily (once in the morning and once in the evening approximately 12 hours apart) orally without regard to food throughout the 6-Month Treatment Period. Subjects randomized into the study will visit the site during the 6-Month Treatment Period on Day 1, and then monthly (28-day

intervals) from Month 1 through Month 6. Additional study visits may occur, either for subjects returning their sanitary products at a Product Collection Visit or for a Premature Discontinuation Visit (if applicable).

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

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

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

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

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

Post-Treatment Follow-Up Period

During the 12-Month Post-Treatment Follow-Up Period, visits will occur either by phone or on-site from Months 1 through 12.

During the Phone Visits (Post-Treatment Follow-up Visits Month 2, Month 4, Month 5, Month 7, Month 8, Month 10 and Month 11), Site Personnel will discuss adverse events, concomitant medications, if applicable, obtain the results of the subject's self-administered urine pregnancy test and will remind subjects of the importance of consistent use of appropriate and effective dual non-hormonal contraception throughout the Post-Treatment Follow-Up Period. Subjects may begin taking hormonal contraceptive preparations only after completing the Post-Treatment Follow-Up Month 2 Visit and following the return to a full menses (menses with full menstrual flow) in the Post-Treatment Follow-Up Period. If the subject's full menses has not returned by the Post-Treatment Follow-Up Month 2 Visit, an adverse event of amenorrhea should be documented.

Subjects will be required to collect sanitary products for their first menses with full menstrual flow in the Post-Treatment Follow-Up Period. If the subject does not return sanitary products for her first full menses, she will be required to collect and return sanitary products for her next full menses. Subjects will return the sanitary products at a Product Collection Visit within approximately 5 days after cessation of bleeding or spotting. The Post-Treatment UBQ will be administered by Site Staff at each Phone or Site Visit until the subject has returned sanitary products from her first full menses in the Post-Treatment Follow-Up Period. Once a subject returns sanitary products from a full menses in the Post-Treatment Follow-Up Period, the Post-Treatment UBQ no longer needs to be completed.

All subjects will be required to have DXA scans at Post-Treatment Follow-Up Months 6 and 12.

Procedures and assessments in the Post-Treatment Follow-Up Period should be performed as specified in Appendix C, Study Activities.

Unscheduled Visit

In the event an Unscheduled Visit is necessary during the Treatment or Post-Treatment Follow-Up Period, the site will perform at minimum, the UBQ and an assessment of adverse events and concomitant medications. For Unscheduled Visits when study drug is dispensed (e.g., to replenish lost or damaged study drug), the subject will also be required to have a negative urine pregnancy test result prior to dispensing. Clinical judgment should dictate when other safety assessments (such as vital signs and/or symptom-directed physical examination) should be conducted and should also support the reason for the Unscheduled Visit.

Visit Windows

Visit windows will be allowed for the monthly visits during the Treatment and Post-Treatment Follow-Up Periods. During the Treatment Period, each subsequent monthly visit should be scheduled based on the date of the Day 1 Visit. At the Month 6 Treatment Period Visit, a –4 or +6 day visit window will be allowed in order to collect sanitary products from the last episode of menstrual bleeding or spotting prior to the Month 6 Visit if menstrual bleeding starts immediately prior to or coincides with the scheduled visit. The subject will be instructed to continue taking study drug from the extra blister card until she returns for the Month 6 Visit.

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

Table 1. Visit and Assessment Windows

Study Visit Windows	
Study Visit	**Visit Windows**
Treatment Period: Months 1 – 5	±4 days
Treatment Period: Month 6	–4 or +6 days
Post-Treatment Follow-Up Period: Months 1 – 12	±7 days
Assessment-Specific Windows for Treatment and Post-Treatment Period	
Study Visit/Assessment	Visit Windows
Treatment Period	
Month 3: Ultrasound, DXA Scan (if applicable)	±7 days
Month 6: Ultrasound, MRI (if participating in MRI subset) DXA Scan and Endometrial Biopsy	–15 or + 4 days
Post-Treatment Follow-Up Period	
Month 3: MRI (if participating in MRI subset)	–15 or +4 days
Month 6: Ultrasound, DXA Scan	–15 or +4 days
Month 12: DXA Scan	–15 or +4 days

5.2 Selection of Study Population

Subjects who completed the 6-Month Treatment Period of their respective Pivotal Study, have signed informed consent and meet eligibility criteria will be eligible for participation into this Extension Study.

Each Investigator will employ their clinical judgment in conjunction with protocol specified inclusion/exclusion criteria to determine if subject meets eligibility. Questions should be directed to the AbbVie Therapeutic Area Medical Director (TA MD) listed in Section 6.1.5 if further clarification is required.

5.2.1 Inclusion Criteria

1. Subject has voluntarily signed and dated the informed consent form (ICF), approved by an Institutional Review Board/Ethics Committee (IRB/EC), prior to initiation of any study-specific procedures.

2. Subject has completed the 6-Month Treatment Period of their respective Pivotal Study (either Study M12-815 or Study M12-817).
3. Subject has BMD decrease < 8% in the spine, total hip and femoral neck at Month 6 of the Treatment Period of their respective Pivotal Study.
4. Subject's urine and/or serum pregnancy test(s) results were consistently negative during the Treatment Period of their respective Pivotal Study and at Day 1 of this Extension Study.
5. Subject must agree to use two forms of non-hormonal contraception (dual contraception) consistently during the Treatment Period and Post-Treatment Follow-Up Period (Subject may start hormonal contraception after completion of the Post-Treatment Follow-Up Month 2 Visit and return to first full menses).

   Acceptable methods of dual contraception include the following combinations:

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

   Subject is not required to use dual contraception methods if:

   - Sexual partner(s) is vasectomized, at least 6 months prior to Screening.
   - Subject practices total abstinence from sexual intercourse, as the preferred lifestyle of the subject; periodic abstinence is not acceptable.
   - Subject had a bilateral tubal occlusion (including ligation and blockage methods such as Essure®), at least 4 months prior to Screening.
   - Subject is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as noted above.
6. Subject's endometrial biopsy from the Month 6 Visit of their respective Pivotal Study shows no clinically significant endometrial pathology.

Rationale for Inclusion Criteria:

1	This is standard criterion in accordance with harmonized Good Clinical Practice (GCP)
2, 3	These criteria were selected to ensure an appropriate subject population of premenopausal women with HMB associated with uterine fibroids (prognostic and predictive)
4, 5	The impact of elagolix on pregnancies or breastfed infants is unknown and there is a possible risk of miscarriage due to changes in hormone levels; therefore, these criteria ensure pregnant women are not enrolled into the study and adequate precautions are taken to avoid pregnancy during study participation (prognostic and risk)
6	This is standard criteria to ensure general good health and the safety of the subjects (risk)

5.2.2 Exclusion Criteria

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

1. Subject met criteria for removal from therapy in her respective Pivotal Study.
2. Subject is planning a pregnancy within the next 18 months.
3. Subject has current suicidal ideation as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the Columbia-Suicide Severity Rating Scale (C-SSRS) completed at Treatment Period Month 6 Visit of her respective Pivotal Study.
4. Subject has a newly diagnosed clinically significant medical condition that requires intervention **OR** an unstable medical condition that makes the subject an unsuitable candidate for the study in the opinion of the Investigator (including, but not limited to, uncontrolled diabetes mellitus, uncontrolled hypertension, epilepsy requiring anti-epileptic medication, unstable angina, confirmed inflammatory bowel disease,

hyperprolactinemia, clinically significant infection or injury or symptomatic endometriosis [confirmed by laparoscopy/laparotomy]).

5. Subject is using any systemic corticosteroids for over 14 days or is likely to require treatment with systemic corticosteroids during the course of the study. Over-the-counter and prescription topical, inhaled, intranasal or injectable (for occasional use) corticosteroids are allowed.

6. Subject, who in the judgment of the Investigator, will be unable or unwilling to comply with study-related assessments and procedures, including collection of sanitary products.

Rationale for Exclusion Criteria:

1, 3, 4, 5	This is standard criteria to ensure general good health and the safety of the subjects (risk)
2	The impact of elagolix on pregnancies or breastfed infants is unknown and there is a possible risk of miscarriage due to changes in hormone levels; therefore, these criteria ensure adequate precautions are taken to avoid pregnancy or breastfeeding while receiving elagolix (risk)
6	This criterion was added to ensure the population of subjects enrolled will comply with study-related procedures and subject collection requirements throughout the entire study (predictive)

5.2.2.1 Concomitant Therapy

Any medications and therapies that were administered in the Pivotal Study and are continuing to be administered at the time of entry into this study should be reviewed, assessed and if applicable, added to the source documents and eCRFs of this Extension Study.

Any new medications or vaccines (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject receives during the Treatment and Post-Treatment Follow-Up Periods must be recorded in source documents and on the

Concomitant Medication eCRFs. The reason for use, date(s) of administration (including start and end dates) and dosage information (including dose and frequency) must be recorded.

5.2.2.2 Iron Supplementation

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

The recommended oral dose of ferrous sulfate is 300 to 325 mg following the diagnosis of anemia. If a subject is unable to tolerate ferrous sulfate then ferrous gluconate, liquid iron or intravenous (IV) iron may be prescribed. If subjects experience constipation from iron supplement use, stool softeners may be prescribed. All iron supplements taken during the study must be recorded on the concomitant medications eCRF.

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

5.2.2.3 Concomitant Use of Corticosteroids

Chronic use (> 14 days) of systemic corticosteroids is prohibited during the Treatment and Post-Treatment Follow-Up Periods; however, inhaled corticosteroids for the treatment of asthma are permitted. Over-the-counter and prescription topical, inhaled, intranasal or injectable (for occasional use) corticosteroids are allowed.

5.2.2.4 Prohibited Therapy

All hormonal forms of birth control (except the emergency contraceptive pill, levonorgestrel 1.5 mg [such as Plan B®], or ulipristal acetate 30 mg [such as Ella® or

EllaOne®]) are prohibited during the Treatment Period and until the Post-Treatment Follow-Up Month 2 Visit and return to first full menses. If subject does not return to menses she must continue use of dual non-hormonal contraception.

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

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

Due to the extensive list of herbal remedies and supplements, please contact the AbbVie TA MD for any that may be prohibited. Generally-speaking, any supplements or herbal remedies used to treat premenstrual or gynecological problems, such as black cohosh, are excluded.

The following medications should not be taken during the Treatment and Post-Treatment Follow-Up Period.

Table 2. Prohibited Medications

Prohibited During the Treatment Period and Post-Treatment Follow-Up Periods	
Hormonal/Anti-Hormonal Medications[%], such as:	GnRH agonists leuprolide acetate (Lupron®), nafarelin acetate (Synarel®), goserlin acetate (Zoladex®) GnRH antagonists (other than elagolix) Danazol (Danocrine®) Medroxyprogesterone acetate (Depo-Provera®, Provera®) Oral contraceptives Estrogen preparations* Testosterone preparations Other progestins* (oral, vaginal, transdermal, implantable, IUD, or LNG-IUS, except emergency contraception) HCG or HCG products Glucocorticoids, oral or injectable (chronic use only) Mifepristone Selective Progesterone Receptor Modulators (e.g., Ulipristal acetate (except as emergency contraception, i.e., 30 mg) and Tamoxifen) Bromocriptine (Parlodel®) Cabergoline (Dostinex®) Raloxifene (Evista®) Aromatase Inhibitors (e.g., Anastrozole [Arimidex®], Exemestane [Aromasin®])
Non-hormonal estrogen supplements[#]	Natural estrogen preparations (e.g., soy-containing supplements, black cohosh)
Antifibrinolytics[%]	Tranexamic acid (Lysteda, Cyklokapron, Cyclo-f)
Moderate or strong CYP3A Inducers,[9] and Anti-epileptic medications, such as:	**Strong Inducers:** St. John's Wort Rifampin Carbamazepine Phenytoin Dexamethasone chronic use **Moderate Inducers:** Bosentan Efavirenz Etravirine Modafinil Nafcillin

Table 2. Prohibited Medications (Continued)

Prohibited During the Treatment Period and Post-Treatment Follow-Up Periods	
Bisphosphonates, RANKL inhibitors, Anabolic Bone Agents or rPTH, such as:	Fosamax®, Fosamax Plus D®, Binosto®, Boniva®, Reclast®, Zomata®, Prolia® XGEVA, Forteo®, Actonel®, Atelvia®, Miacalcin®, Fortical®
Synthetic Prostaglandin E1 (PGE1) Analogs, such as:	Misoprostol (Cytotec®, Arthrotec®) Single use of PGE1 for cervical preparation prior to biopsy is allowed; chronic use is prohibited
Oral Retinoids (topical applications are permitted), such as:	Accutane® (isotretinoin)

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

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

% Subjects may begin the use of hormonal contraceptives or tranexamic following completion of the Post-Treatment Follow-Up Month 2 Visit and she has returned to first full menses. Tranexamic acid, if necessary can be prescribed following completion of the Post-Treatment Follow-Up Month 2 Visit and return to first full menses.

If a prohibited medication is necessary to treat an adverse event or a pre-existing condition other than uterine fibroids, the AbbVie TA MD noted in Section 6.1.5 should be consulted; however, if clinically required and to prevent an immediate hazard to the subject being treated, the AbbVie TA MD should be notified as soon as possible after the start of use. Additionally, if a subject takes a prohibited medication during the study, except as permitted per protocol (hormonal medication taken after completion of the Post-Treatment Follow-Up Month 2 Visit and return to first full menses), her continued participation in the study will be evaluated by the Investigator and the AbbVie TA MD. If there are any questions regarding prior or concomitant therapy, please contact your Study Monitor.

5.2.3 Contraception Recommendations and Pregnancy Testing

Contraception Counseling/Dispense Contraceptives

Subjects (excluding those subjects who have had a bilateral tubal ligation or bilateral tubal occlusion) will continue to be counseled at every visit throughout their participation in the study on the importance of pregnancy prevention and the use of appropriate and effective

methods of birth control during the Treatment and Post-Treatment Follow-Up Periods of the Extension Study.

Subjects must agree to use two forms of non-hormonal contraception (dual contraception) consistently throughout the Treatment Period and Post-Treatment Follow-Up Periods (Subjects may begin the use of hormonal contraception (e.g., oral or IUD) after completing the Post-Treatment Follow-Up Month 2 Visit and have returned sanitary products for a full menses).

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

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

Subjects are not required to use dual contraception methods if:

- Sexual partner(s) is vasectomized at least 6 months prior to Screening
- Subject practices total abstinence from sexual intercourse, as the preferred lifestyle of the subject; periodic abstinence is not acceptable
- Subject had a bilateral tubal occlusion (including ligation and blockage methods such as Essure®) at least 4 months prior to Screening.
- Subject is not sexually active with men; periodic sexual relationship(s) with men requires the use of dual non-hormonal contraception as indicated above.

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

- Completed the Post-Treatment Follow-Up Month 2 Visit and
- Returned sanitary products for a full menses in the Post-Treatment Follow-Up Period

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

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

1. The informed consent form will include an attestation requiring the subject to confirm in writing her full awareness that the potential risks of study drug (elagolix) on the unborn child are unknown and therefore she must not get pregnant during the entire time of study participation, and that she agrees to consistently use dual non-hormonal contraception throughout her study participation (during the Treatment and Post-Treatment Follow-Up Period.
2. The Investigator or designated study staff will counsel the subject that the study drug is not contraceptive, that ovulation may occur even though the study drug may have altered menstrual cyclicity, and that fetal abnormalities have been observed in women who have received elagolix in clinical studies that were not deemed to be related to elagolix based on the totality of data; however, it is unknown whether these abnormalities were the result of taking elagolix.
3. The Sponsor will provide training materials to the sites for instructing subjects on the types of protocol-allowed contraception methods, their effectiveness and proper use.
    - The Sponsor will provide sites with a supply of materials to promote pregnancy prevention, including contraceptives (condoms and spermicides), and lubricants to provide to subjects at no charge. Subjects should only use the pregnancy prevention materials provided by the Sponsor as these products have undergone analytical testing by the analytical lab to confirm there is no or limited interference with the alkaline hematin method.
    - Subjects will be allowed to choose a contraception method of their choice from the contraceptives provided by the Sponsor and practice the allowable methods of dual contraception. The site will assess the subject's basic understanding of

the proper use through discussion and demonstration of proper techniques, including proper diaphragm use.

- The site will dispense contraceptives to subjects throughout Treatment and through the Post-Treatment Follow-Up Period, as needed. Subjects may begin the use of hormonal medication after completion of the Post-Treatment Follow-Up Month 2 Visit and return to first full menses.
- The source documents will capture date contraception counseling was performed, whether the subject is sexually active with men, the type of contraceptive used, a change in contraceptive method, use of a non-study supply brand, contraceptives provided to the subject, and the date supplies were provided.
- As appropriate, the subject will be asked to attest by signature at the time of consent, and in a stand-alone attestation form at Day 1 and at the Month 6 or Premature Discontinuation study visit that allowable methods of contraception, as described during the pregnancy prevention counseling, are being practiced.
- For subjects who have had a bilateral tubal occlusion, attestation is only required to be collected once at the time of consent.

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

Pregnancy Tests and Reporting a Pregnancy

Urine and/or serum pregnancy tests will be performed as specified in Appendix C, Study Activities, in all subjects regardless of sexual activity status or method of contraception.

The subject must have a confirmed negative urine pregnancy test within 24 hours prior to performing endometrial biopsy or SIS (if applicable).

The urine and serum pregnancy tests performed at the Final Treatment Visit (Month 6 or Unscheduled Visit just prior to roll-over into the Extension Study) of the Pivotal Study will serve to assess subject eligibility for entry into this Extension Study and the urine pregnancy test result must be reviewed and determined to be negative prior to registering the subject in IRT. If the Final Treatment Visit in the Pivotal Study (just prior to roll-over into this Extension Study) does not occur on the same day as Day 1 of this Extension Study, a urine pregnancy test must be performed at Day 1 and a negative urine pregnancy test result must be obtained prior to administration of the first dose of study drug in this Extension Study.

Urine pregnancy test results must be negative prior to providing subjects with their Day 1 and subsequent supply of study drug, (including an Unscheduled Visit at which study drug is dispensed).

Home pregnancy test kits will be provided to the subject at the Day 1 Visit and Month 6 or Premature Discontinuation Visit during the Treatment Period when logistically, a urine pregnancy test cannot be performed at the study site or other medical facility within 24 hours prior to an endometrial biopsy or SIS (if applicable). The subject must self-administer and report a negative urine pregnancy test result to the site within 24 hours prior to undergoing these procedures.

A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. The subject should temporarily discontinue study drug administration while waiting for the results of the serum pregnancy test. If a serum pregnancy test result is positive at any time during the Treatment Period, the site will immediately inform the subject to discontinue study drug (Section 6.1.6). If a subject is confirmed as pregnant, the subject will be prematurely discontinued from the study.

An ultrasound examination will be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery if the subject becomes pregnant during the Treatment or Post-Treatment Follow-Up Periods of the study. Refer to Section 6.1.6 for instructions on reporting of a pregnancy to the Sponsor and the required follow-up on the subject/fetus and live infant births.

5.3 Efficacy, Pharmacokinetic, Pharmacodynamic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures during the Treatment and Post-Treatment Follow-Up Periods described in this protocol are summarized in Appendix C, Study Activities.

5.3.1.1 Study Procedures

Subjects entering into this Extension Study will have completed all Month 6 study procedures in their respective pivotal study, Studies M12-815 or M12-817, and following availability of all assessment results, the subject will have been determined to be eligible for this Extension Study.

Study procedures in this Extension Study begin on Day 1 and should be conducted as per Appendix C, Study Activities. When the Day 1 Visit occurs on the same day as the Final Treatment Visit of the respective Pivotal Study, assessments and procedures performed at the Final Treatment Visit should not be repeated at the Day 1 Visit of this Extension Study, unless deemed necessary by the Principal Investigator.

The study procedures outlined in Appendix C, Study Activities, are discussed in detail in this section, with the exception of the monitoring of study drug accountability (Section 5.5.7) and the collection of concomitant medication and adverse event information (Section 5.2.2.1 and Section 6.1, respectively). Study data will be recorded on eCRFs with the exception of several PRO questionnaires that will be recorded on source documents and on eCRFs.

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

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

When findings of past medical, surgical, gynecological or uterine fibroid history are identified, the relevant eCRF(s) and Source Note(s) of the Pivotal Study (Studies M12-815 or M12-817) should be updated, unless otherwise instructed by the Monitor.

Informed Consent

The IRB/IEC approved informed consent will be signed by the subject before beginning any study-specific procedures. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Gynecological (Pelvic and Breast) Examination

A complete breast, and pelvic examination, including external genitalia will be performed during the Month 6 or Premature Discontinuation Visit in the Treatment Period.

Pap Test

A Pap test will be performed at Treatment Period Month 6 or Premature Discontinuation Visit.

A Pap test will be collected using the Thin Prep® Pap Test™ provided and analyzed by the central laboratory. If the subject is experiencing menstrual bleeding that precludes the

performance of the Pap test, this procedure should be performed as soon as possible after the menstrual bleeding has ended. In the case of an unsatisfactory sample, the Pap test should be repeated. The repeat Pap test should be performed when the subject is not experiencing menstrual bleeding.

Subjects who have Pap test results that require additional evaluation should follow local guidelines or standard of care. In addition, the AbbVie TA MD should be notified to discuss subject's management plan for any clinically significant pathologic findings during the Post-Treatment Follow-Up Period.

All subjects will continue in the Post-Treatment Follow-Up Period. Subjects who may require colposcopy will enter the Post-Treatment Follow-Up Period and should be treated per local guidelines or standard of care.

Endometrial Biopsy

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

Pre-medication for the endometrial biopsy procedure is allowable and should be recorded in source documents and on the appropriate eCRF. Misoprostol for cervical dilatation is allowable. An office hysteroscopy may be performed to obtain the endometrial biopsy sample if the endometrial biopsy cannot be performed because of anatomical reasons.

An endometrial biopsy will be performed at the Treatment Period Month 6 Visit or at the Premature Discontinuation Visit (if the subject prematurely discontinues after the Month 3 Visit).

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.

In the event that the Month 6 or Premature Discontinuation Visit endometrial biopsy cannot be performed (e.g., due to a stenotic cervix or location of fibroids), or an insufficient biopsy sample is obtained and the concurrent TVU indicates a thickness of > 4 mm, a repeat biopsy must be performed. If upon repeat, a sample cannot be obtained or remains insufficient, the AbbVie TA MD should be consulted.

Subjects with abnormal endometrial pathology results at Treatment Month 6 will enter the Post-Treatment Follow-Up Period and should be managed according to standard of care. The subject's management plan for any of these significant pathologic findings should be reviewed with the AbbVie TA MD, and the subject outcome documented in the eCRF.

Physical Examination

During the Treatment Period and Post-Treatment Follow-Up Periods, a complete physical examination will be performed at Treatment Period Month 6 and Post-Treatment Follow-Up Month 6 or Premature Discontinuation Visits. The complete physical examination will include weight measurements. Symptom-directed physical examinations will be performed as specified in Appendix C, Study Activities.

Any clinically significant physical examination findings will be recorded in the source documents and in the eCRFs as adverse events.

Vital Signs

Vital sign determination of heart rate, blood pressure, respiratory rate and body temperature will be obtained at all visits during the study as indicated in Appendix C, Study Activities. The blood pressure and heart rate measurements should be taken prior to scheduled blood collections. Body temperature measurements should be assessed using

the same modality consistently throughout the study, e.g., oral, aural, axillary, etc., and the modality will be reported in the source documents and eCRF.

12-Lead Electrocardiogram (ECG)

During the Treatment Period, a resting 12-lead ECG will be conducted at the Month 6 Visit or Premature Discontinuation Visit (if applicable) as indicated in Appendix C, Study Activities.

The Investigator or qualified designee at the study site will determine if any findings outside the normal physiological variation are clinically significant (in consultation with a cardiologist if necessary), and document this on the ECG tracing/report with signature and date. The original ECG tracing or a certified copy of the original tracing with the physician's assessment will be retained in the subject's records at the study site. For ECG with QT interval corrected for heart rate (QTc) > 450 msec, the correction formula used (i.e., Bazett's or Fridericia's) and the corrected result should be recorded in source documents and eCRF. The study site should use the same correction formula used in the respective pivotal study and continue to consistently use throughout this study.

Mammogram

All subjects who had a mammogram performed to determine eligibility into their respective Pivotal Study, will have a mammogram performed at Treatment Period Month 6 or at the Premature Discontinuation Visit if it has been approximately 12 months since the screening mammogram was performed.

Central Imaging Procedures

Fibroid and uterine assessments will be obtained using pelvic ultrasound (TAU and TVU) throughout the study. In addition to the TAU and TVU, an MRI will continue to be performed in the subset of subjects who consented and participated in the MRI Subset during their respective pivotal study. The MRI subset will continue to evaluate uterine fibroid size and volume and uterine volume using another technique in addition to ultrasound.

All ultrasound and MRI images will be sent to the Central Imaging Core Lab (ICL) for review to monitor safety during the Treatment and Post-Treatment Follow-Up Periods.

The pelvic ultrasound (TAU, TVU) and/or SIS and MRI (if applicable) will be performed by the Investigative Sites' or affiliated Radiology Department. The Ultrasonographer at each Investigative Site will be required to acquire the ultrasound and MRI (if applicable) images according to the Imaging Acquisition Guidelines provided by the ICL. Images should be sent/transmitted to the ICL for subject evaluation during the course of the study. Refer to the Image Acquisition Guidelines for instructions on submitting images to the ICL.

The pelvic ultrasound (TAU, TVU), and/or SIS and MRI (if applicable) will be assessed both locally and by the ICL. If images are unevaluable, the ICL will inform the Investigative Site and additional images will need to be resubmitted. If there is a discrepancy between the local assessment and the central reader's assessment, this should be brought to AbbVie's attention and AbbVie will discuss the findings with the local site and central reader on a case-by-case basis. The Investigator or designee should consult the local ultrasound and SIS reports and/or images in order to make any safety-related judgments concerning the subject. The interpretation of the local report and/or images will be filed or recorded in the subject's source documents. Data and/or local interpretation from the local ultrasound and SIS images will not be recorded in the eCRF unless associated with a significant finding or adverse event.

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

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

Pelvic Ultrasound: TAU and TVU

Pelvic ultrasounds (TAU and TVU) will be performed at Treatment Period Month 3 and Month 6 and at Post-Treatment Follow-Up Period at Month 3 and Month 6 or at the time of premature discontinuation (if not performed within the past 2 months). Assessments for the pelvic ultrasound include, but are not limited to the following:

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

Magnetic Resonance Imaging (MRI) Subset:

Subjects who participated in the MRI subset in the Pivotal Studies will continue to be included in the MRI subset in this study.

An MRI will be performed at the Month 6 or Premature Discontinuation Visit during the Treatment Period and at the Post-Treatment Follow-Up Month 3 Visit. Subjects who had an MRI performed in the past 3 months prior to prematurely discontinuing are not required to repeat the MRI at the time of Premature Discontinuation during the Treatment or Post-Treatment Follow-Up Period.

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

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

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

Intracavitary Uterine Findings

An SIS may be performed during the Treatment or Post-Treatment Follow-Up Periods when the pelvic ultrasound (TAU and TVU) or MRI (if applicable) results suggest an intracavitary lesion such as a polyp. The finding of a polyp during the Treatment or Post-Treatment Follow-Up Periods should be documented as an adverse event if the Investigator considers it to be clinically significant.

The AbbVie TA MD should be notified of the subject's management plan for any clinically significant pathologic findings during the Treatment and Post-Treatment Follow-Up Periods.

Ovarian Findings:

During Treatment or Post-Treatment Follow-Up 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 adverse event if the Investigator considers them to be clinically significant.

Bone Mineral Density (DXA Scan)

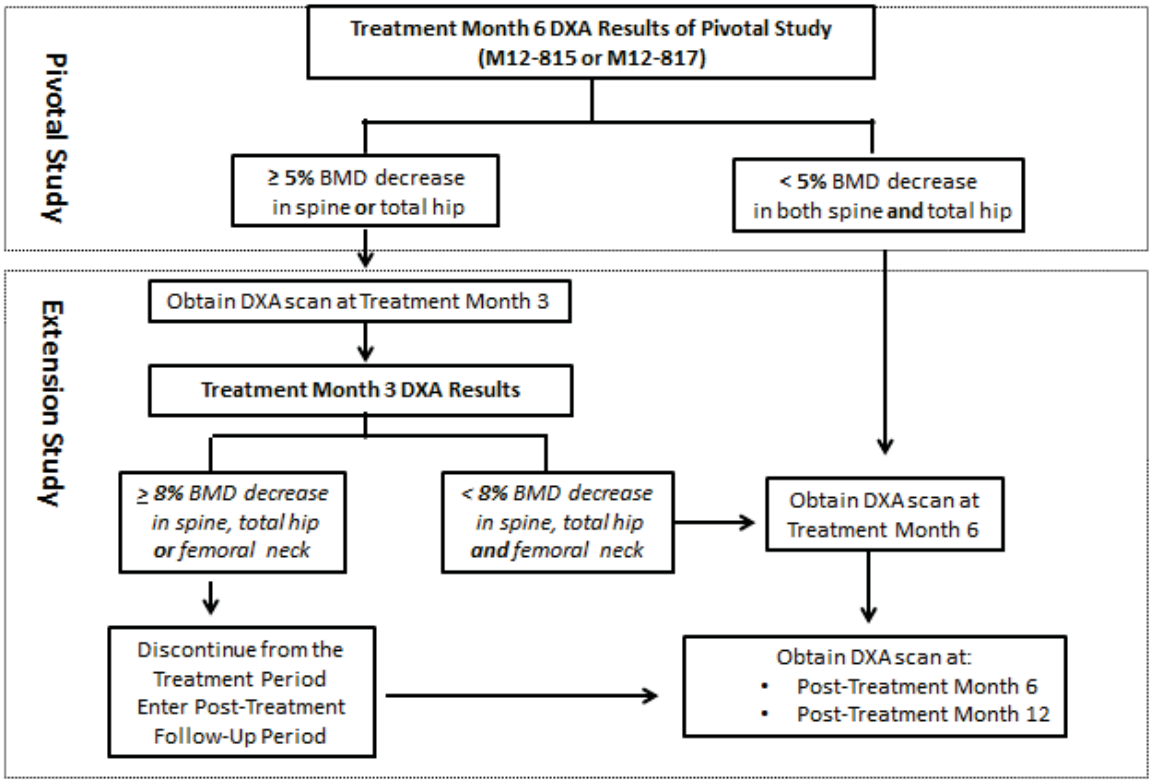
DXA scans of the spine, femoral neck and total hip will continue to be performed by qualified technologist/radiologists utilizing GE Lunar or Hologic equipment and sent to an ICL for review and analysis. The same instructions on calibration and standardization of instruments as used in the pivotal studies and as specified in the manual provided to all study sites should be used.

DXA Scans Performed in the Treatment Period

DXA scans are required to be performed during the Treatment Period as follows:

- Month 3: Only for those subjects with BMD decrease ≥ 5% in the spine **or** total hip at Month 6 of their respective pivotal study (Studies M12-815 or M12-817) as determined by the central reader
- Month 6: All subjects

Figure 2. Management of BMD % Decrease: Treatment Period and Post-Treatment Period



Management of BMD % Decrease on DXA scan obtained at **Treatment Month 3**:

- Subjects with BMD decrease ≥ 8% in the spine, femoral neck **or** total hip will discontinue study drug treatment and enter the Post-Treatment Follow-Up Period to have the required BMD evaluation at Follow-Up Months 6 and 12.
- Subjects with BMD decrease ≥ 5% and < 8% in the spine **or** total hip will continue in treatment and will require a DXA scan at Treatment Month 6.

DXA Scans Performed in the Follow-Up Period

DXA scans will be performed in the Follow-Up Period as follows:

- Follow-Up Month 6
- Follow-Up Month 12
- Follow-Up Premature Discontinuation visit **unless** the subject prematurely discontinued from Follow-Up and had a study DXA scan within approximately 1 month prior to the Follow-Up Premature Discontinuation Visit.

Management of BMD % Decrease from Baseline for Subjects Who Prematurely Discontinue in the Follow-Up Period

Subjects who prematurely discontinue at the time of or after the Month 3 study visit will and have a Follow-Up Premature Discontinuation DXA scan performed will be referred to a bone specialist for further evaluation utilizing the criteria listed below for referral at the end of the 12 Month Follow-Up Period.

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

Management of subjects with BMD % decrease at Post-Treatment Follow-Up Month 12 is outlined below and illustrated in Figure 3.

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

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

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

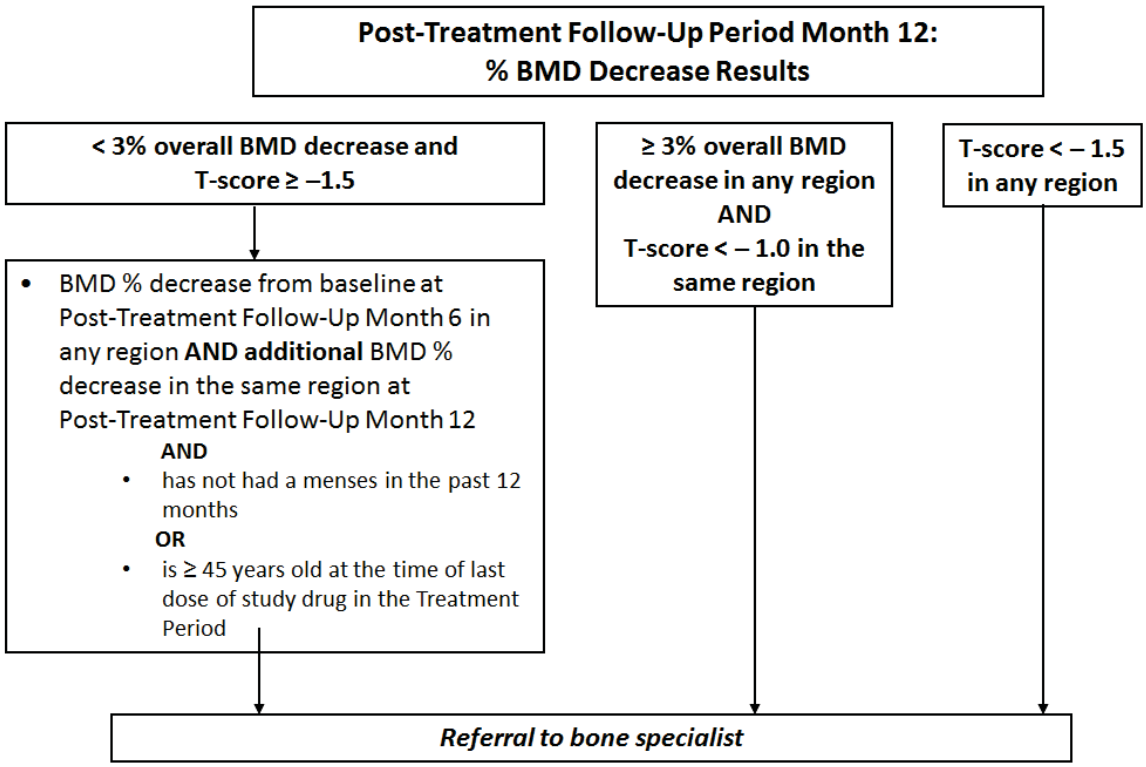
    OR

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

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

Subjects who do not meet any of the above criteria will not require additional BMD follow-up.

Figure 3. Management of BMD % Decrease: Post-Treatment Follow-Up Month 12



Note: If criteria is not met, no referral to bone specialist is required.

The baseline DXA is the Screening DXA performed in the respective Pivotal Study M12-815 or Study M12-817. In the event that there is a change in DXA machine for a subject between baseline and a subsequent time-point, the AbbVie TA MD must be consulted.

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

Clinical Laboratory Tests

Samples will be obtained for the laboratory tests listed in Table 3, at the time points indicated in Appendix C, Study Activities.

Table 3. Clinical Laboratory Tests

Hematology	**Clinical Chemistry (After Minimum 8-Hour Fast)**	**Urinalysis**
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands (if indicated) Lymphocytes Monocytes Basophils (if indicated) Eosinophils (if indicated) Platelet count (estimate not acceptable) Mean Cell Volume of RBC (MCV) Mean Corpuscular Hemoglobin (MCH) Mean Corpuscular Hemoglobin Concentration (MCHC)	Sodium Potassium Chloride Bicarbonate Serum creatinine Glucose Calcium Inorganic phosphorus Magnesium Total protein Albumin Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALAT) Serum glutamic-oxaloacetic transaminase (SGOT/ASAT) Alkaline phosphatase Uric acid Lactate dehydrogenase Creatinine Phosphokinsae Serum iron Serum ferritin Total iron binding capacity (TIBC)	Specific gravity Ketones Protein Blood Glucose pH Microscopic Exam
		Urine[%]
		Gonorrhea Chlamydia
		Lipid Panel (After Minimum 8-Hour Fast)
		LDL cholesterol HDL cholesterol Triglycerides Total cholesterol
		Lipid Profile
		Apolipoprotein A and B
Pregnancy Test		
Serum pregnancy		
Endocrine Panel		**PK and PD Assay**
Follicle-stimulating hormone (FSH) Luteinizing Hormone (LH) Reflexive Thyroid Stimulating Hormone (TSH) Thyroxine Binding Globulin (TBG)		Elagolix and NETA* E2 and P*

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

% Optional – ordered at Investigator's discretion.

All laboratory samples (hematology, chemistry, urinalysis, endocrine panel, lipid panel) will be assessed using a certified central laboratory and these data will be used for data analysis. The central laboratory will provide instructions regarding the collection (including any fasting requirements), processing and shipping of samples. Blood draws should be performed after vital signs and ECG recordings are conducted at a visit. All clinical laboratory samples will be shipped to the central laboratory, with the exception of the venous blood sample for alkaline hematin analysis which will be sent to the alkaline hematin laboratory. Residual serum samples remaining after chemistry testing has been performed will be stored frozen at the central laboratory for possible repeat testing or further analysis upon AbbVie's request.

The laboratory results (except Apo A and Apo B) will be provided by the central laboratory to the Investigative Site where they will be reviewed, signed and dated by the Investigator. For any value outside of the reference range, the Investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). The Investigator will assess clinically significant laboratory values per standard of care which may include repeating the test to verify the out-of-range value. Clinically significant laboratory abnormalities may be documented as adverse events, depending on the interpretation of the Investigator (Section 6.1).

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

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

Safety Laboratory Tests

Clinical safety laboratory tests consist of hematology, clinical chemistry, including lipid panel and urinalysis samples. The clinical chemistry and lipid panel samples should be obtained in the morning following an overnight fast (minimum of 8 hours); however, there may be circumstances when a sample was not under fasting conditions. If a sample

was obtained with less than 8 hours of fasting, the Source Documents and the lab requisition should be marked to indicate that the sample was obtained under non-fasting conditions.

Lipid Panel

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

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

Blood samples for Apo A and Apo B will be collected as part of the Chemistry Panel. The Apo A and Apo B data are exploratory and results will not be provided to the Investigative Site.

Urine Test for Gonorrhea and Chlamydia (Optional)

Gonorrhea and chlamydia testing can be ordered at the Investigator's discretion to test for active gonorrhea or chlamydia. Any treatment provided will occur outside of the protocol.

Endocrine Panel

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

Sanitary Product Collection for Alkaline Hematin Assay

Quantitative measurement of the volume of MBL will be performed using the alkaline hematin method. Menstrual blood loss will be assessed in all subjects using validated sanitary products, also referred to as "validated" products. Validated products have undergone analytical testing by the analytical lab to confirm adequate precision and

accuracy of blood recovery as well as no or limited interference with the alkaline hematin method.

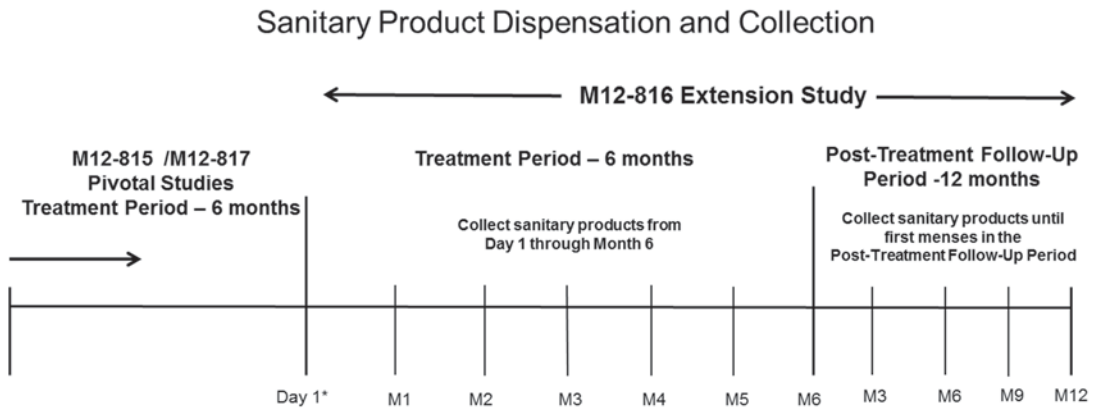
Subjects will continue to collect their sanitary products throughout the 6-Month Treatment Period and up through their first menses with full menstrual flow in the Post-Treatment Follow-Up Period to assess return to menses. Subjects will be dispensed sanitary collection kits that consist of validated sanitary products, product collection bags, bar-coded labels and a keg with screw-on lid for storage as provided by the vendor. It is important that only the sanitary products provided for use during the study are used. Validated sanitary products may include:

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

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

The dispensation and collection requirements in the Treatment and Post-Treatment Follow-Up Periods are outlined in Figure 4.

Figure 4. Sanitary Product Dispensation and Collection



* Dispense sanitary products and sanitary product collection kits as needed at all visits starting with Day 1, including Product Collection Visits
- All products should be returned to the study site within approximately 5 days after all bleeding and/or spotting has ended
- Product Collection during Treatment Period and Post-Treatment Follow-Up Period will continue to be collected through the first menses in the Post-Treatment Follow-Up Period

Sanitary Product Collection During the Treatment Period

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

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

Treatment Period Product Collection Visits

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

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

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

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

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

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

Return of Sanitary Products to Alkaline Hematin Vendor

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

Home Visits

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

Use of Non-Validated Products

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

Patient Reported Outcomes (PRO) Rating Scales

As in the Pivotal Studies, Site Personnel will be trained on all rating scales used in this study. The objective of this training is to establish uniformity across sites in administration of these rating instruments. The following questionnaires will continue to be completed by the Subjects and/or the Investigator or Site Staff, as appropriate at the time points indicated in Appendix C, Study Activities. Subjects and Site Staff will be asked to record their responses directly onto paper questionnaires and enter into the eCRF.

Uterine Bleeding Questionnaire (Treatment-UBQ)

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

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

Subjects who have not collected and returned sanitary products for their first menses with full menstrual flow in the Post-Treatment Follow-Up Period, will be asked at each visit

before sanitary products are returned if they had any bleeding or spotting since their last visit. If the subject did not have uterine bleeding or spotting the site staff will indicate "No" on the UBQ. If the subject did have bleeding or spotting, the subject will be asked the reason she did not return the sanitary product collection keg. This response will be recorded on the UBQ (Appendix E) by the Site Staff.

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

The UFS-QoL (Appendix F) is a disease-specific self-administered questionnaire used to measure health-related quality of life in women with symptomatic uterine fibroids. Each subject will be asked to complete a modified (4-week recall) UFS-QoL Questionnaire[10] to report fibroid-related symptoms experienced during the previous 4 weeks.

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

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

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

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

Work Productivity and Activity Impairment Questionnaire (WPAI)

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

EuroQol-5D 5 level (EQ-5D-5L™)[11]

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

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a systematically administered instrument developed to track suicidal adverse events across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. During the Treatment Period, the C-SSRS, Since Last Visit (Appendix K) questionnaire will be administered as specified in Appendix C, Study Activities.

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 notify the AbbVie TA MD. Appropriate steps will be taken to protect the subject (including possible discontinuation from the study and referral for appropriate psychiatric care). The C-SSRS will be administered at the times outlined in Appendix C, Study Activities.

Health Care Resource Utilization (HCRU)

The Health Care Resource Utilization questionnaire (Appendix L) will be used to capture routine/general health care visits (that are not associated with an adverse event) to non-study Health Care Providers during the Treatment Period. Subjects will be asked to provide information on any visits to non-study Health Care Practitioners in the past 4 weeks for routine/general health visits including any diagnostic or therapeutic

procedures that were performed. The responses will be recorded on the HCRU by the Site Staff. Health care resource use related to an Adverse Event or Serious Adverse Event will be captured as part of the Adverse Event, independent of the HCRU, and recorded in the eCRF.

Phone Contact During Follow-Up Period

During the Follow-Up Period at Follow-Up Months 2, 4, 5, 7, 8, 10, and 11, Site Staff will telephone subjects to assess ongoing adverse events, concomitant medications, provide contraception counseling and obtain the result of the subject-administered urine pregnancy test. Site staff will also assess return to full menses and administration of the Post-Treatment UBQ as applicable. The phone call and pregnancy test result will be documented in source documents and eCRF.

Randomization and Assignment of Subject Numbers

The site will contact IRT to assign the subject to the Extension Study once the subject has signed the informed consent and meets all eligibility criteria for the Extension Study. Only subjects randomized to placebo in the Pivotal Study will be randomized at Day 1 by IRT to receive either elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD.

The same subject number assigned in the Pivotal Study will be used to identify the subject throughout the Extension Study. The site will register the Day 1 Visit in IRT to dispense the first study drug kit for the Extension Study.

During the Treatment Period, sites will register each monthly visit in IRT in order to obtain a scheduled re-supply of study drug to dispense to each subject. In the event study drug becomes lost or damaged, the site can contact IRT to obtain an unscheduled re-supply of study drug kit numbers to dispense. Sites will register subjects as "Completed" or "Discontinued" (if the subject prematurely discontinues) at the end of the Treatment Period and will also register Post-Treatment Follow-Up Month 6 and Month 12 Visits or Premature Discontinuation from Post-Treatment, if applicable.

5.3.1.2 Collection and Handling of Pharmacodynamic Variables

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

A single blood sample will be collected at each timepoint indicated in Appendix C, Study Activities, to be used for the pharmacodynamic analysis of estradiol and progesterone. The blood samples for assay of estradiol and progesterone will be collected in one 9 mL evacuated collection tube without anticoagulant (red cap, no gel separators to be used). Sufficient blood volume will be collected to provide approximately 4 mL serum from each sample. Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

Estradiol and progesterone samples will be collected at all visits indicated in Appendix C, Study Activities, and drawn at any time during the visit. The date and time of collection will be recorded on the central laboratory requisition form.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood Samples for Elagolix and Norethindrone Assay

Blood samples for assay of elagolix and norethindrone, also known as PK samples, will be collected by venipuncture into 3 mL evacuated K_2-ethylenediaminetetraacetic acid (K_2EDTA)-containing collection tubes at the time points indicated in Appendix C, Study Activities. Sufficient blood will be collected to provide approximately 1 mL plasma from each sample.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing and shipment. Elagolix and norethindrone samples will be collected at all visits indicated in Appendix C, Study Activities, and drawn at any time during the visit. The date and time of collection will be recorded on the central laboratory requisition form.

5.3.2.2 Measurement Methods

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

5.3.3 Efficacy Variables

5.3.3.1 Primary Efficacy Variable

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

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

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

5.3.3.2 Secondary Efficacy Variable

The following will be considered secondary variables:

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

5.3.4 PRO and Quality of Life Variables

- UFS-QoL Questionnaire

- EuroQol (EQ-5D-5L) Questionnaire
- Health Care Resource Utilization (HCRU) Questionnaire
- Patient Global Impression of Change (PGIC) Questionnaires
- Work Productivity and Activity Impairment (WPAI) Questionnaire

5.3.5 Safety Variables

- Change from baseline to Month 6 in bone mineral density measured by DXA
- Number and percentage of subjects reporting treatment-emergent adverse events (TEAEs)
- Number and percentage of subjects reporting adverse events of special interest (AESI) (e.g., hypoestrogenic adverse events)
- Time to the first Post-Treatment menses
- Change from baseline in clinical laboratory parameters
- Change from baseline in vital signs
- Endometrial biopsy and pelvic ultrasound findings
- Columbia Suicide Severity Rating Scale (C-SSRS)

5.3.6 Pharmacodynamic Variables

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

5.3.7 Pharmacokinetic Variables

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

5.3.8 Independent Data Monitoring Committee

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

5.4 Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a subject from the study at any time if the Investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol. Subjects who withdraw from the study will not be replaced. Each subject will be withdrawn from the study if any of the following occur:

- The subject decides to withdraw consent for any reason.
- The investigator believes it is in the best interest of the subject.
- Clinically significant deterioration of the subject's medical status as determined by the investigator.
- The subject requires surgical intervention for treatment of uterine fibroids and menstrual bleeding or other procedures including hysterectomy, myomectomy, uterine artery embolization, high intensity focused ultrasound (HIFU), endometrial ablation, dilation and curettage (D&C), etc. during the Treatment Period. In the post treatment period these procedures do not warrant withdrawal if performed during the Post-Treatment Period unless a hysterectomy with bilateral salpingo-oophorectomy (BSO) is performed and the Subject does not plan to use Hormone Replacement Therapy within 1 month of the surgery date.
- The subject becomes pregnant.

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

5.4.1 Discontinuation of Individual Subjects

In the event that a subject withdraws or is prematurely discontinued from study drug treatment, the subject should complete the Treatment Period Premature Discontinuation Visit as soon as possible (preferably within 2 days of last dose of study drug, if possible) and undergo study procedures as outlined in Appendix C, Study Activities. Subjects who prematurely discontinue during the Treatment Period are expected to enter the 12-Month Post-Treatment Follow-Up Period, unless discontinuing due to pregnancy. Each subsequent monthly Post-Treatment Follow-Up Period Visit should be scheduled based on the date of the last dose of study drug.

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

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

If a subject becomes pregnant during the Treatment or Post-Treatment Follow-Up Periods, no additional study procedures, except an ultrasound will be conducted. Refer to Section 6.1.6 for instructions on reporting of a pregnancy to the Sponsor and the required follow-up on the subject/fetus and live births.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is clinically significant (as determined by the Investigator), the Investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The Investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

The following procedures for study discontinuation will be followed:

- If the Sponsor has decided to prematurely discontinue the study, the Sponsor will promptly notify in writing the Investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- The Investigator must promptly notify the IRB/IEC and give detailed reasons for the discontinuation.
- The Investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of the treatment regimen, if applicable, by other appropriate regimens.

5.4.3 Treatment Interruption

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

- Adverse event, that based on clinical judgment, requires temporary suspension of treatment or prevents a subject from taking study drug
- Due to malfunction of barrier contraception or unprotected intercourse

Additionally, there may be times when a subject has had treatment interruption due to having forgotten to take study drug, lost study drug, etc. If the subject has missed 7 or more consecutive days of dosing (with either ABT-620 or elagolix plus E2/NETA), the AbbVie TA MD must be consulted to determine whether the subject may resume study drug administration or continue in the Treatment Period.

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

5.5 Treatments

5.5.1 Treatments Administered

Subjects on active treatment in the Pivotal Studies will be assigned by IRT to receive the same treatment, either elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD, for an additional 6 months in the Extension Study. Subjects on placebo in the Pivotal Studies will be randomly assigned by IRT to receive elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA (estradiol 1 mg/norethindrone acetate 0.5 mg) QD in a 1:1 ratio for a total of 6 months of treatment. The treatment administration is presented in Table 4 below.

Table 4. Treatments Administered

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

Study drug consisting of elagolix and E2/NETA or placebo will each be supplied in a carton. The subject will be instructed to self-administer the first dose of study drug approximately 12 hours after their last dose taken as part of the Pivotal Study. In addition, Subject will be instructed to self-administer their study drug throughout the 6-Month Treatment Period.

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

Study drug will be taken orally twice daily for the entire 6-Month Treatment Period. A morning dose of 1 tablet of elagolix and 1 capsule of (E2/NETA) or matching placebo and an evening dose of 1 tablet of (elagolix) should be taken each day approximately 12 hours apart. Study drug should be taken with approximately 8 oz. (240 mL) of water without regard to food. Study drug should be taken at approximately the same time each morning and evening in order to promote compliance.

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

On days when the subject visits the study site for the scheduled visits, she will take her morning dose at home, prior to the visit. The evening dose will be taken from the newly dispensed supply of study drug. Subjects must return all study drug containers at each monthly visit.

When during the Treatment Period, a monthly visit occurs > 28 days since the last visit, the subject will be instructed to continue taking study drug from the extra blister card (1 week supply) until she returns for the next month's visit.

5.5.2 Identity of Investigational Products

Information about the drug formulations to be used in this study is presented in Table 5.

Table 5. Identity of Investigational Products

Study Drug	Formulation	Route of Administration	Trademark	Manufacturer
Elagolix	Film-coated 300 mg tablets	Oral	N/A	AbbVie
E2/NETA*	Estradiol 1 mg/ Norethindrone acetate 0.5 mg capsules*	Oral	N/A	Commercial Tablets: Pharmaceutics International, Inc
Matching E2/NETA Placebo	Placebo capsules	Oral	N/A	AbbVie

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

5.5.2.1 Packaging and Labeling

AbbVie will supply study drug in monthly kits (i.e., cartons). Two kits of study drug will be provided at each dispensing visit. One kit consists of elagolix and the other kit consists of E2/NETA capsules or matching placebo capsules. Each kit contains 5 blister cards, with each blister card containing 7 days of study drug. There are 4 weekly blister cards and 1 extra medication blister card in each kit to supply enough medication for 4 weeks (28 days) plus an extra week of dosing.

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

The kits will be assigned to a subject via IRT and will encode the appropriate study drug to be dispensed at the subject's corresponding study visit.

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

5.5.2.2 Storage and Disposition of Study Drugs

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

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

5.5.3 Method of Assigning Subjects to Treatment Groups

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

Subjects will retain the unique subject number assigned to each subject by the IRT during the Pivotal Study M12-815 or Study M12-817. This unique subject number will be used for each subject throughout this study.

Subjects who received placebo in the Pivotal Study M12-815 or Study M12-817 will be randomly assigned to receive elagolix alone or elagolix plus E2/NETA via assignment of a unique randomization number in IRT. The Site Personnel, Investigator, and the Sponsor do not see this information while the study is ongoing. Hence, there is no unblinding concern related to the assignment of the unique randomization number in this Extension Study. Subjects who received elagolix alone or elagolix plus E2/NETA in the Pivotal Study M12-815 or Study M12-817 will continue to receive the same dose of active drug in this study.

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.

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

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses used for this study is discussed in Section 5.6.4. Subjects who received placebo in their respective Pivotal Study will be randomized into one of the two treatment groups as described in Section 5.5.1. Subjects who received active treatment in their respective Pivotal Study will continue to be assigned to receive the same treatment they received during the pivotal study.

Study drug will be initiated at the study site on Day 1. Subjects will be instructed to self-administer study drug twice a day (once in the morning and once in the evening approximately 12 hours apart) with approximately 8 oz (240 mL) of water. Subjects must return all study drug containers (used or unused) at the subsequent visit.

5.5.5 Blinding of Investigational Product

The elagolix dose will be provided open label and each active E2/NETA dose will be identical in appearance to its matched placebo. The study site personnel and subject will remain blinded to each subject's treatment throughout the course of the study. The IRT will provide access to blinded subject treatment information during the study.

AbbVie must be notified before the blind is broken, unless identification of the study drug is required for medical emergency; i.e., situation in which the knowledge of the specific blinded treatment will affect the immediate management of the subject/patient's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documents and eCRF, as applicable. AbbVie will remain blinded until the database of the 6-month Treatment Period is locked.

5.5.6 Treatment Compliance

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

The Investigator or his/her designated and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than those described in the protocol.

Subjects should be advised of the importance of treatment compliance. Study drug should be taken consistently at approximately the same time in the morning and evening each day. Daily recordings of study drug dosing will be obtained using a compliance packaging blister card for all subjects (for both elagolix and E2/NETA/matching placebo). AbbVie will provide training and study drug compliance materials to sites for instructing subjects on study drug compliance.

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

Sites should instruct subjects not to remove extra or multiple medications from the blister cards all at once and should only remove the study drug from the blister when it is the time to take the dose. If the compliance data shows incidence of removing a number of extra medications, sites should re-train the subjects on the importance of only removing study drug when it is time to take the dose and record re-training in the source documents.

During review of the study drug compliance with the study subject, if the number of tablets/capsules to be taken and the number of tablets/capsules returned do not add up to the number of tablets/capsules dispensed, an explanation should be provided by the subject and recorded in the source documents.

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

Compliance packaging data will be used for exposure response analysis.

5.5.7 Drug Accountability

The study Investigator or designee will verify by signature and date that study drug supplies are received intact and in the correct amounts indicated on the shipping document Proof of Receipt or similar shipping document or via direct recording in IRT. The shipment receipt must be acknowledged in IRT in order to become available for dispensation to subjects. The IRT must also be contacted when any subject discontinues study drug.

The IRT will maintain a current and accurate inventory of all clinical drug supplies, accountability, reconciliation, returns and destruction for each site. The IRT will also include the lot number, kit number, Proof of Receipt number, the number of blister cards/cartons dispensed, initials of person who dispensed the drug, and the date study drug was dispensed for each subject. In addition to using IRT inventory, an accurate inventory of study drug can also be kept by the site.

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

The study Investigator or his/her designated representative agrees not to supply study drug to any persons not enrolled in the study or not named as a Sub-Investigator.

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

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This Phase 3 extension study will be conducted as a double-blind, multi-center, study in premenopausal women with HMB associated with uterine fibroids. This study will continue to evaluate the safety and efficacy of elagolix 300 mg BID alone and elagolix

300 mg BID in combination with E2/NETA QD (1 mg/0.5 mg). The elagolix alone arm in this extension study is being used as a reference arm in order to better understand the effects of add-back therapy on safety and efficacy parameters. This allows a benchmark for efficacy, as well as safety in regards to BMD and hypoestrogenic effects. In addition, for a long term treatment, this will allow a better understanding of elagolix alone, as well as activella.

5.6.2 Appropriateness of Measurements

The safety assessments used in this study are standard, widely used and generally recognized as reliable, accurate and relevant within the context of this study design.

Heavy menstrual bleeding is the most common symptom of women with uterine fibroids. The quantitation of menstrual blood loss using the alkaline hematin method on sanitary products has been validated by the analytical testing laboratory. Pelvic ultrasound is a standard method for assessing uterine fibroid size, and fibroid and uterine volume. Endometrial biopsy is a standard method for assessing endometrial safety. DXA is the established gold standard method to assess changes in BMD.

5.6.3 Suitability of Subject Population

Premenopausal women with HMB (> 80 mL per menstrual cycle) and uterine fibroids were selected for this study because that is the population who suffer from HMB associated with uterine fibroids. No studies in males or in females outside of the reproductive years are necessary for this proposed indication.

5.6.4 Selection of Doses in the Study

This is an extension study to the pivotal studies, Studies M12-815 and M12-817, therefore the doses used in this extension study are the same as those used in the pivotal Studies with the exception that subjects randomized to placebo in their respective pivotal study will be re-randomized to active treatment, either elagolix 300 mg BID alone or elagolix 300 mg BID in combination with E2/NETA QD in a 1:1 ratio, therefore all subjects in this

extension study will receive active treatment. The maximum elagolix dose administered in this study will not exceed a total daily dose of 600 mg.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Section 6.1 through Section 6.1.5. For product complaints, please refer to Section 6.2.

All adverse events will be followed to a satisfactory conclusion.

6.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The Investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the Investigator will provide an Other cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities, and vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention and/or if the investigator considers them to be adverse events.

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

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

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed

earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events of Special Interest

Some adverse events, such as adverse events of special interest (AESI), such as rash/hypersensitivity, fracture, neuro-psychiatric (depression, mood swings, etc.), vasomotor symptoms (hot flush, night sweats) or serious adverse events. AbbVie may require additional information, including family history, to be collected and recorded in the eCRF.

6.1.2 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each adverse event:

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

6.1.3 Relationship to Study Drug

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

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

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

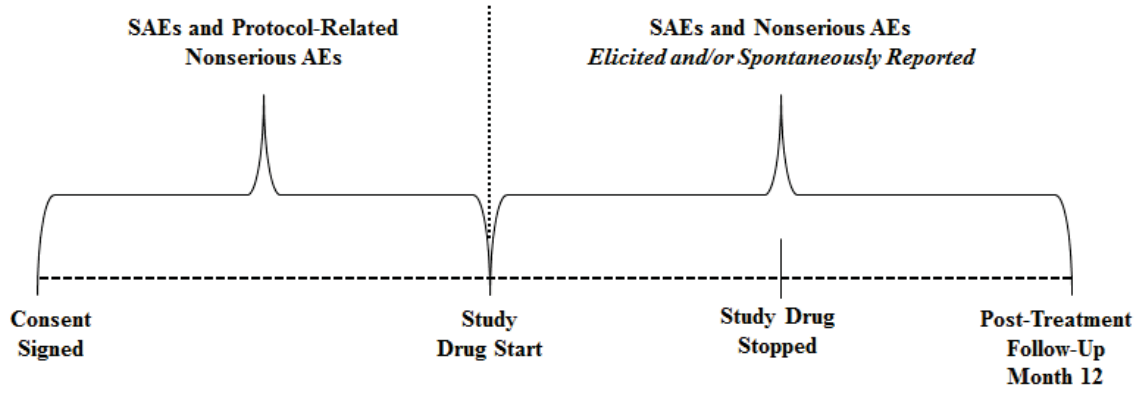
6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration through Month 12 in the Post-Treatment Follow-Up Period, (if applicable) will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

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

Adverse event information will be collected as shown in Figure 5.

Figure 5. Adverse Event Collection



6.1.5 Adverse Event Reporting

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

Email: [redacted]

FAX to: [redacted]

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

Men's and Women's Health Safety Team

AbbVie
1 North Waukegan Road
North Chicago, IL 60064

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

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

Primary Therapeutic Area Medical Director:

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

Phone: [redacted]
Fax:
Cell:
Email:

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

Phone: [redacted]
Email: [redacted]

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the Treatment or Post-Treatment Follow-Up Periods of the study must be discontinued (Section 5.4 and Section 5.4.1). A positive urine pregnancy test result must be confirmed with a serum pregnancy test. If a serum pregnancy test result is positive at any time during the Treatment Period of the study, the site will immediately inform the subject to discontinue study drug. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for any study subject with a positive serum pregnancy test from the signing of the informed consent through the Post-Treatment Follow-Up Period. The site will report a positive pregnancy test to the Sponsor, will follow the course of the subject's pregnancy, and report to the Sponsor on the health of the subject and fetus at each trimester and at the first post-delivery pediatrician visit.

If the subject becomes pregnant during the Treatment or Post-Treatment Follow-Up Periods of the study, an ultrasound examination will be performed as early as possible during the first trimester of pregnancy to assess the conception date and document an intrauterine pregnancy. The following information on the outcome of the pregnancy that occurred after signing of the informed consent, regardless of when the subject became pregnant (i.e., either during the Treatment or Post-Treatment Follow-Up Periods) should be collected: fetal outcome (e.g., spontaneous or elective abortion, live infant or still birth), date of delivery, birth weight, birth length, gender, birth defects, congenital anomaly and medically significant complications during pregnancy or labor or delivery. For live infant births, information on the health of the infant will be collected 6 to 12 months after delivery.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality by the product to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and recorded in source documents as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

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

Primary Contact:

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

Phone: [redacted]
Fax:
Cell:
Email:

Alternate Contact:

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

Office: [redacted]
Fax:
Email:

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

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

8.1.1 General Considerations

The SAS system will be used to perform the statistical analyses. Unless otherwise specified, no statistical comparisons will be performed. Statistical comparisons that are

performed will be two-sided and a significance level of 0.05 will be used. A test will be deemed statistically significant if the *P* value rounded to three decimal places is less than or equal to 0.05 unless otherwise specified.

Separate summaries will be provided for each of the following groups of subjects.

1. Subjects randomized to elagolix 300 mg BID in the Pivotal Studies M12-815 or M12-817 and continued to receive elagolix 300 mg BID in the Extension Study;
2. Subjects randomized to elagolix 300 mg BID plus E2/NETA QD in the Pivotal Studies M12-815 or M12-817 and continued to receive elagolix 300 mg BID plus E2/NETA QD in the Extension Study;
3. Subjects randomized to placebo in the Pivotal Studies M12-815 or M12-817, and re-randomized to elagolix 300 mg BID in the Extension Study;
4. Subjects randomized to placebo in the Pivotal Studies M12-815 or M12-817, and re-randomized to elagolix 300 mg BID plus E2/NETA QD in the Extension Study.

8.1.2 Data Sets Analyzed

Full Analysis Set

The full analysis set is comprised of all subjects who took at least one dose of the study drug in this Extension Study. The full analysis set will be used for all efficacy analyses unless otherwise specified in the Statistical Analysis Plan (SAP).

Safety Analysis Set

The safety analysis set includes all subjects who took at least one dose of the study drug in the Extension Study M12-816. All safety analyses will be performed based on the safety analysis set unless otherwise specified in the SAP.

8.1.3 End-of-Treatment Period Analysis

An end-of-treatment period analysis of efficacy, demographic and safety variables will be performed after all subjects enrolled in this study completes the 6-Month Treatment Period of this Extension Study M12-816. This end-of-treatment period analysis will include all Treatment Period data from all subjects enrolled into the Extension Study. The data base will be versioned and any discrepant data will be clarified before the lock. The analyses will be completed by the Clinical Statistics Department at AbbVie.

8.1.4 Independent Data Monitoring Committee

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

8.1.5 Demographic, Baseline Characteristics and Concomitant Medications

Subjects initially randomized to placebo in the Pivotal Studies M12-815 or M12-817 will have their baseline (except for the MBL volume) re-set to the last non-missing assessments collected prior to the first dose of elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD in this Extension Study, unless otherwise specified. Subjects initially randomized to elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD in the Pivotal Studies M12-815 or M12-817 will have their baseline refer to the baseline from the respective Pivotal Studies M12-815 or M12-817, unless otherwise specified. Exceptions will be specified in the SAP.

For the MBL volume, the baseline for all subjects will refer to the baseline from Pivotal Studies M12-815 or M12-817.

Baseline characteristics will be summarized for each treatment group.

Demographic characteristics will be summarized by treatment group.

The duration of study drug will be summarized by treatment group.

Protocol deviations and reasons for discontinuation will be summarized.

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

8.1.6 Time Points, Time Windows and Time Periods for Analysis

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

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

8.1.7 Efficacy

Data will be summarized separately for each of the treatment groups of subjects described in Section 8.1.1.

8.1.7.1 Primary Efficacy Variable

8.1.7.1.1 Primary Analysis

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

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

The primary analysis of the primary endpoint will be performed using the full analysis set which is comprised of all subjects who took at least one dose of the study drug in this Extension Study.

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

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

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

The percentage of subjects with MBL volume < 80 mL at the Final Month and 50% or greater reduction in MBL volume from baseline to the Final Month in the Extension Study will be summarized by treatment group.

8.1.7.1.2 Derivation of Primary Efficacy Endpoint

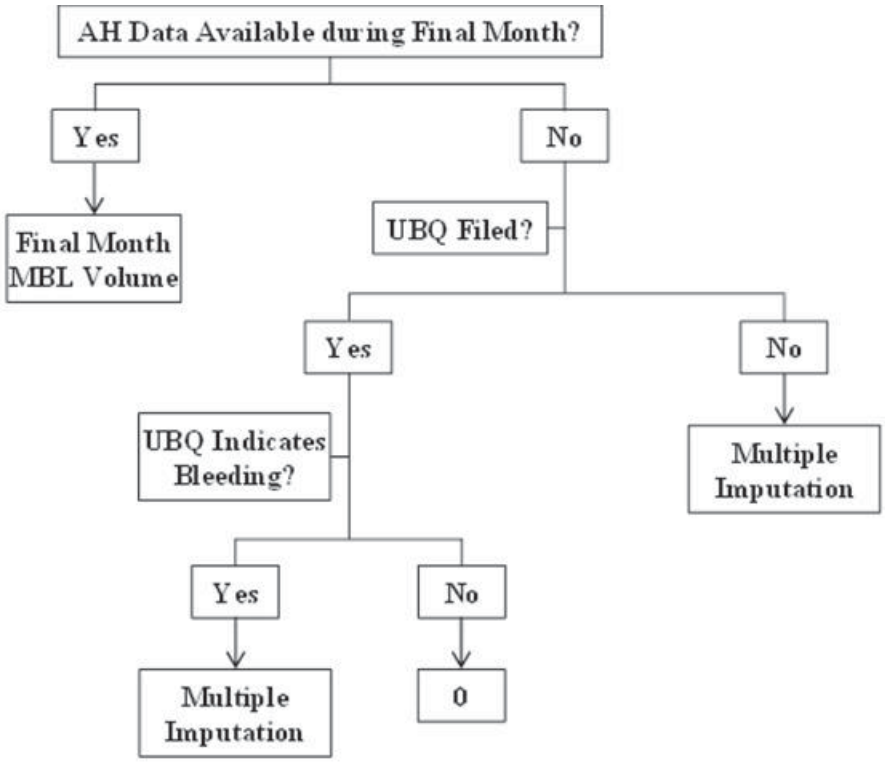
The Final Month MBL volume will be derived as follows:

- If a subject has any evaluable AH data reported during the Final Month (i.e., she has at least 1 day of AH data during the last 28 days of treatment), then her primary endpoint will be based on AH data during the Final Month. The subject's Final Month MBL volume will be the total MBL volume which is the sum of the observed MBL volume over the last 28 days of treatment.

- If a subject is missing the Final Month AH data and the Uterine Bleeding Questionnaire is completed, then:
  - A value of 0 will be assigned to the Final Month MBL volume if no bleeding or spotting, "Subject only had spotting that did not require the use of sanitary products" or "There was no visible blood on the sanitary products" is indicated on the Uterine Bleeding Questionnaire (Appendix D).
- Otherwise, the primary endpoint will be imputed using multiple imputation as described in Section 8.1.7.1.3.

A flow-chart showing how the primary endpoint will be derived is presented in Figure 6.

Figure 6. Flow-Chart for Deriving Primary Endpoint



8.1.7.1.3 Multiple Imputation

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

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

Each subject's responder status will be derived based on the imputed Final Month MBL volume from the *M* imputed datasets. The percentage of responders will be summarized by treatment group.

8.1.7.1.4 Sensitivity Analysis of the Primary Efficacy Variable

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

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

8.1.7.2 Secondary Efficacy Variables

The secondary efficacy measures during the Treatment Period of the Extension Study include the following:

- Change and percent change from baseline in MBL volume to each month and to the Final Month;
- Percentage of subjects with suppression of bleeding (no bleeding allowed, spotting allowed) at the Final Month;

- Percentage of subjects with baseline hemoglobin ≤ 10.5 g/dL who have an increase in hemoglobin > 2 g/dL at Month 6.

8.1.7.3 Other Efficacy Variables

- Percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline during 28-day intervals throughout the Treatment Period;
- Percentage of subjects with amenorrhea;
- Percentage of subjects with control of bleeding;
- The bleeding days;
- Change and percent change from baseline in hemoglobin concentration;
- PGIC for Menstrual Bleeding and Non-Bleeding Uterine Fibroid Symptoms;
- Change and percent change from baseline in fibroid and uterine volume;
- Change from baseline for the UFS-QoL;
- Change from baseline for the EuroQoL-5D (EQ-5D-5L);
- The HCRU;
- Change from baseline for the WPAI.

Analysis details will be specified in the SAP.

8.1.7.3.1 Reduction of Bleeding

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

The change and percent change from baseline in MBL volume to each month and to the Final Month, will be summarized for each treatment group. The percentage of subjects with suppression of bleeding and the percentage of subjects with amenorrhea will be

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

The change and percent change from baseline to monthly intervals in number of bleeding days will be summarized by treatment group.

8.1.7.3.2 Hemoglobin Concentration

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

8.1.7.3.3 Fibroid and Uterine Volume

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

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

8.1.7.3.4 Quality of Life

UFS-QoL

Improvement in quality of life will be assessed on the UFS-QoL Questionnaire (4-week recall). The change from baseline will be calculated and summarized for each of the UFS-QoL subscales (symptom severity, concern, activities, energy/mood, control, self-conscious and sexual function) and the UFS-QoL total.

EQ-5D-5L

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

The change from baseline in subject health status will be summarized for each treatment group.

8.1.7.3.5 Patient Global Impression of Change (PGIC)

PGIC for Menstrual Bleeding (PGIC-MB):

PGIC-MB is to assess the change in subjects' severity of menstrual bleeding. The number and percentage of subjects in each response category based on PGIC-MB will be summarized by treatment group.

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

PGIC-NBUFS is to assess the severity of overall non-bleeding symptoms and the severity of specific non-bleeding uterine fibroid symptoms. The number and percentage of subjects in each response category of each question based on PGIC-NBUFS will be summarized by treatment group.

8.1.7.3.6 Work Productivity and Activity Questionnaire (WPAI)

The change from baseline for the WPAI will be summarized for each treatment group.

8.1.7.3.7 Health Care Resource Utilization Questionnaire (HCRU)

HCRU will be summarized for each treatment group.

8.1.7.3.8 Multiple Comparisons

No statistical tests will be performed to test the differences between the active treatment arms. Therefore no multiplicity adjustment is required.

8.1.8 Safety

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

8.1.8.1 General Considerations

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

Data will be summarized separately for each of the treatment groups of subjects described in Section 8.1.1.

8.1.8.2 Adverse Events

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

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

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

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

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

8.1.8.3 Analysis of Laboratory Data and Vital Signs

Changes from the baseline to each visit in continuous laboratory and vital sign parameters will be summarized by treatment group.

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

Analysis details will be specified in the SAP.

8.1.8.4 Bone Mineral Density

The within-group percent change from baseline to Month 6 in the Extension Study in BMD will be summarized for each treatment group with mean, standard deviation, median and two-sided 95% confidence interval.

For subjects randomized to placebo in the Pivotal Studies M12-815 and M12-817, their BMD baseline will be re-set to the last data collected prior to the first dose of either elagolix 300 mg BID or elagolix 300 mg BID plus E2/NETA QD in this Extension Study. For subjects randomized to either elagolix 300 mg BID or elagolix 300 mg BID plus

E2/NETA QD in the Pivotal Studies M12-815 and M12-817, the BMD data from the Pivotal Studies will be included in the analysis, and baseline for these subjects will refer to the baseline from the Pivotal Studies M12-815 or M12-817.

For subjects who have at least 12 months of total exposure to elagolix, the percent change from baseline to Month 6 in the Extension Study in BMD will be compared between elagolix dose groups (elagolix 300 mg BID versus elagolix 300 mg BID plus E2/NETA QD) using analysis of covariance (ANCOVA) with treatment as the main effect and baseline BMD as a covariate. A two-sided 95% confidence interval will be constructed for the between-group difference in percent change from baseline to Month 6 in the Extension Study in BMD. Additionally, the mixed model repeated measures (MMRM) method for analyzing percent change in BMD will be conducted as appropriate.

The number and percentage of subjects with categorized percent change from baseline to Month 6 in the Extension Study in BMD ($\leq 0\%$, $> 0\% - \leq 1.5\%$, $> 1.5\% - \leq 3\%$, $> 3\% - \leq 5\%$, $> 5\% - < 8\%$, or $\geq 8\%$) will be summarized for each treatment group. Analysis details will be specified in the SAP.

8.1.8.5 Post-Treatment Analysis of Menstruation

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

8.1.8.6 Endometrial Biopsy

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

8.1.8.7 Pelvic Ultrasound

The number and percentage of subjects with complex ovarian cysts > 3.5 cm, as well as the number and percentage of subjects with simple ovarian cysts > 5 cm will be summarized for each treatment group at each time point. The change from baseline to

Month 6 in the Extension Study in endometrial thickness will be summarized for each treatment group.

8.1.8.8 Columbia Suicide Severity Rating Scale (C-SSRS)

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

8.1.9 Pharmacokinetic/Pharmacodynamic Analysis

Plasma concentrations of elagolix and norethindrone and serum concentrations of estradiol, progesterone, luteinizing hormone and follicle stimulating hormone will be listed for each subject by visit day and dose regimen, as applicable. Pharmacokinetic data may be combined with data from other studies in women. Exposure-response analyses may be conducted as appropriate. For example, if pharmacokinetic exposures are estimated, analyses may be conducted to assess the relationship of pharmacokinetic parameters and estradiol and progesterone concentrations, versus efficacy and safety. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The two Pivotal Studies M12-815 and M12-817 have a planned enrollment of a total of 800 subjects. Based on assumptions related to discontinuation in the Pivotal Studies and the estimated roll over rate into this Extension Study, approximately 400 subjects are expected to be enrolled in this Extension Study.

9.0 Ethics

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

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the

ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

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

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

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source

documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

For all adverse events, the onset date and event description will be captured in source documents. Other adverse event data points required for eCRF completion can be entered directly in the eCRF and may serve as the source document and should be printed and signed and dated by the Investigator/designated physician.

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

10.2 Case Report Forms

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

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

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

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

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

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

11.0 Data Quality Assurance

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

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

The AbbVie monitor or designee will monitor the study site throughout the study. A source document review will be performed against entries on the eCRFs and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, ongoing review of the data will be conducted by a physician or representative at AbbVie.

Data entered into eCRFs will be electronically transferred to AbbVie and imported into the database using validated software throughout the study. Computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Routine hematology, serum chemistry, lipid and endocrine panels, urinalysis, Pap smears and endometrial biopsies will be analyzed using a central laboratory. The data from these analyses will be electronically transferred from the central laboratory to the study database.

A review of all laboratory results will be conducted by a physician and clinical review team at AbbVie, the AbbVie monitors (or their representatives), the investigator and other appropriate personnel from AbbVie.

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

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

Pelvic ultrasound, SIS and MRI scans will be read by the Central Imaging Vendor. The results of these scans will be electronically transferred from the Central Imaging Vendor to the study database.

DXA scans will be read by a Central DXA Reader. The results of these scans will be electronically transferred from the Central DXA Reader to the study database.

12.0 Use of Information

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

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of elagolix. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

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

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

13.0 Completion of the Study

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

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

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report. The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for elagolix (ABT-620).
2. I have read this protocol and agree that the study is ethical.
3. I have read the Package Insert/Product Label for E2/NETA.
4. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
5. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
6. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	Extension Study to Evaluate the Efficacy and Safety of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids
Protocol Date:	18 December 2017

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
		Global Drug Supply Management
		Clinical Operations
		Clinical Pharmacokinetics
		Bioanalysis
		Clinical Development
		Data and Statistical Sciences

Appendix C. Study Activities – Treatment Period and Post-Treatment Follow-Up Period

Treatment Period

Procedure	Treatment Period[a]									
	Day 1[b]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[c]	Unsch Visit	PD (if appl)
Informed Consent	X[d]									
Gynecological (External Genitalia, Pelvic and Breast) Examination							X			X
Pap Test							X			X
Endometrial Biopsy							X[e]			X[e,f]
Complete Physical Examination Including Weight							X			X
Symptom-Directed Physical Examination		X	X	X	X	X				
Vital Signs (Temp, BP, Pulse, RR)		X	X	X	X	X	X	X		X
12-Lead Electrocardiogram (ECG)							X			X
Mammogram							X[g]			X[g]
Pelvic Ultrasound: TAU, TVU				X[h]			X[h]			X[h,i]
MRI (Subset of Subjects)							X[h]			X[h,j]
DXA Scan				X[k]			X			X[i]
Dispense Sanitary Products and Collection Kit (Keg, Collection Bags, etc.) as Needed	X	X	X	X	X	X	X	X		X
Collect and Return Sanitary Products and Draw Venous Blood Sample		X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X		X

Procedure	Treatment Period[a]									
	Day 1[b]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[c]	Unsch Visit	PD (if appl)
UBQ		X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]	X[m]
Clinical Safety Labs: Chemistry, Lipid Panel and Hematology		X	X	X	X	X	X			X
Clinical Safety Labs: Chemistry Creatinine Phosphokinase							X			X
Clinical Safety Labs: Urinalysis				X			X			X
Apolipoprotein A and B				X			X			X
Endocrine: FSH and LH		X	X	X	X	X	X			X
Endocrine: Reflexive TSH and Thyroxine-Binding Globulin (TBG)				X			X[n]			X[n]
Pharmacodynamic Sample: Serum Estradiol (E2) and Progesterone (P)		X	X	X	X	X	X			X
Pharmacokinetic Sample (PK): Elagolix and NETA Plasma Concentration		X	X	X	X	X	X			X
Urine Pregnancy Tests	X[o]	X[p,q]	X[p,q]	X[p,q]	X[p,q]	X[p,q]	X[q]	X		X
Serum Pregnancy Tests							X			X
Contraception Counseling/Dispense Contraceptives as Necessary	X[r]	X	X	X	X	X	X	X		X
Birth Control Attestation	X						X			X

Procedure		Treatment Period[a]									
		Day 1[b]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[c]	Unsch Visit	PD (if appl)
PRO Questionnaires	EQ-5D-5L							X			X
	UFS-QoL				X			X			X
	Work Productivity and Activity Questionnaire (WPAI)							X			X
	PGIC-MB		X		X			X			X
	PGIC-NBUFS		X		X			X			X
	Health Care Resource Utilization (HCRU)		X	X	X	X	X	X			X
	C-SSRS – (Since Last Visit)	X[r]	X	X	X	X	X	X			X
Interactive Response Technology (IRT)[p]		X	X	X	X	X	X	X			X
Study Drug Dispense		X	X	X	X	X	X				
Drug Accountability			X	X	X	X	X	X			X
Adverse Event Monitoring		X[r]	X	X	X	X	X	X	X	X	X
Concomitant Medication Review and Update		X[p,r]	X	X	X	X	X	X	X	X	X

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

b. Day 1 will be performed only after all study procedures are completed and results available from the Final Treatment Visit of the Pivotal Study M12-815 or Study M12-817.

c. Product Collection Visit (PCV) is to occur approximately 5 days after cessation of bleeding or spotting and is only necessary if a monthly visit is not scheduled to occur within approximately 5 days after cessation of bleeding or spotting.

d. Protocol-specific informed consent must be obtained prior to the initiation of any Extension Study procedures.

e. Subject must have a confirmed negative urine pregnancy test within 24 hours prior to the endometrial biopsy or SIS (if applicable).

f. Subjects who had an endometrial biopsy performed in the 3 months prior to prematurely discontinuation are not required to have an endometrial biopsy performed at the Premature Discontinuation Visit.

g. All subjects who had a Mammogram in the Pivotal Study will have a mammogram performed at Month 6 or at the Premature Discontinuation Visit if it has been approximately 12 months since the screening mammogram was performed.

h. An SIS may be performed if any new finding on the pelvic ultrasound (TAU and TVU) or MRI results suggest an intracavitary lesion such as a polyp. Refer to Section 5.3.1.1, Study Procedures, for further instruction.

i. Procedure does not need to be performed at the Premature Discontinuation Visit if performed within the past 1 month.

j. Subjects participating in the MRI subset: An MRI does not need to be performed at the Premature Discontinuation Visit if performed within the past 3 months.

k. DXA scan to be performed as outlined per Figure 2, Management of BMD % Decrease: Treatment Period.

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

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

n. TBG only.

o. Day 1 urine pregnancy test: Sample must be collected and a negative test result must be available prior to administration of study drug, unless a urine pregnancy test (with a negative tests result) was performed at the Final Treatment Visit (Month 6 or Unscheduled Visit) of the Pivotal Study **and** the Final Treatment Visit occurs on the same day as Day 1.

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

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

r. Sample or procedure or assessment does not need to be collected or performed when the Final Treatment Visit of the Pivotal Study occurs on the same day as the Day 1 Visit of this Extension Study; the test results and documentation that the procedure was performed must be captured in Source and in the Extension Study eCRFs.

Study Activities – Post-Treatment Follow-Up Period

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

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

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

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

b. Subjects who had an MRI performed in the past 3 months prior to prematurely discontinuing are not required to have an MRI performed at the Premature Discontinuation Visit.

c. DXA Scan to be performed as outlined in Figure 3 for Management of BMD % Decrease during the Post-Treatment Follow-Up Month 12.

d. Procedure does not need to be performed at the Premature Discontinuation Visit if performed within the past 1 month.

e. Safety labs at Post-Treatment Follow-Up Month 12: Lipid Panel only.

f. A positive urine pregnancy test result must be confirmed with a quantitative serum pregnancy test. For any subject who has a positive serum pregnancy test result, a TVU must be performed during the first trimester of pregnancy to assess the gestational age and estimated date of delivery.

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

h. Subject should return sanitary products within approximately 5 days after cessation of bleeding or spotting from the first menses with full menstrual flow in the Post-Treatment Follow-Up Period at a Product Collection Visit or a scheduled site visit. The venous blood sample will be sent with collected products to the Alkaline Hematin laboratory.

i. Post-Treatment UBQ will only be completed when a Subject has not returned sanitary products for a full menses in the Post-Treatment Follow-Up Period.

j. Subjects are required to continue the use of two forms of non-hormonal birth control. Subjects may begin the use of hormonal contraception in place of non-hormonal birth control after completing the Month 2 Visit in the Post-Treatment Follow-Up Period and the subject has returned products for one full menses.

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

Appendix D. Uterine Bleeding Questionnaire – Treatment Period – SAMPLE

(To be Completed by Site Staff)

Version 2.0

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

☐ No ☐ Yes

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

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

☐ There was no visible blood on sanitary products*

☐ Subject forgot to/did not collect*

☐ Subject/Site discarded the sanitary products*

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

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

☐ Other

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

Appendix E. Uterine Bleeding Questionnaire Post-Treatment Follow-Up Period – SAMPLE

(To be Completed by Site Staff)

Version 2.0

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

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

☐ **No** ☐ **Yes**

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

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

☐ There was no visible blood on sanitary products*

☐ Subject forgot to/did not collect*

☐ Subject/Site discarded the sanitary products*

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

☐ Subject collected sanitary products and did not bring them in yet; will return sanitary products at a later date

☐ Other

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

Appendix F. UFS-QoL – SAMPLE

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

Date: _____

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

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

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

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

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

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

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

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

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

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

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

1. Since I started taking study medication, my **abdominal or pelvic pain** has/is
   - ☐ Very much improved
   - ☐ Much improved
   - ☐ Minimally improved
   - ☐ Not changed
   - ☐ Minimally worse
   - ☐ Much worse
   - ☐ Very much worse
2. Since I started taking study medication, my **abdominal or pelvic pressure** has/is
   - ☐ Very much improved
   - ☐ Much improved
   - ☐ Minimally improved
   - ☐ Not changed
   - ☐ Minimally worse
   - ☐ Much worse
   - ☐ Very much worse
3. Since I started taking study medication, my **abdominal or pelvic cramping** has/is
   - ☐ Very much improved
   - ☐ Much improved
   - ☐ Minimally improved
   - ☐ Not changed
   - ☐ Minimally worse

- ☐ Much worse
- ☐ Very much worse

4. Since I started taking study medication, my **back pain** has/is
   - ☐ Very much improved
   - ☐ Much improved
   - ☐ Minimally improved
   - ☐ Not changed
   - ☐ Minimally worse
   - ☐ Much worse
   - ☐ Very much worse
5. Since I started taking study medication, my **abdominal bloating** has/is
   - ☐ Very much improved
   - ☐ Much improved
   - ☐ Minimally improved
   - ☐ Not changed
   - ☐ Minimally worse
   - ☐ Much worse
   - ☐ Very much worse
6. Overall since I started taking study medication, my **non-bleeding symptoms** have/are
   - ☐ Very much improved
   - ☐ Much improved
   - ☐ Minimally improved
   - ☐ Not changed
   - ☐ Minimally worse
   - ☐ Much worse
   - ☐ Very much worse

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

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

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

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

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

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

   _____ HOURS

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

   _____HOURS

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

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

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

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

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

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

CIRCLE A NUMBER

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

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

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

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

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

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

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

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

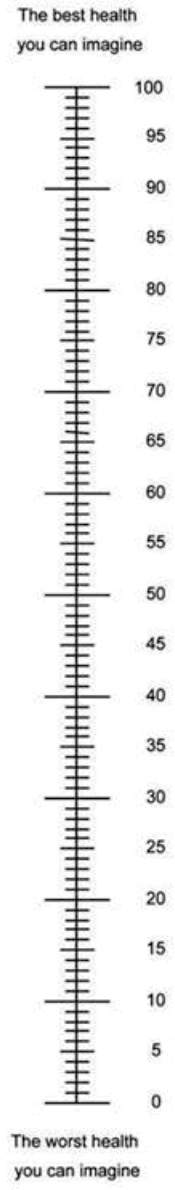
ANXIETY / DEPRESSION

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

SAMPLE

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

YOUR HEALTH TODAY= ☐



SAMPLE

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

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SUICIDAL IDEATION

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

Since Last Visit

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

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

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

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

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

INTENSITY OF IDEATION

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

Most Severe

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

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

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

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

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

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

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

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Appendix L. Health Care Resource Utilization Questionnaire HCRU Version 2.0 – SAMPLE

(To be completed by Site Staff)

Non-Study Visits for Routine/General Health Care

Version 2.0

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

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

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

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

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

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

Health Care Resource Utilization Questionnaire HCRU – SAMPLE

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

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
		☐ NEPHROLOGIST	
		☐ NEUROSURGEON	
		☐ NURSE	
		☐ NURSE PRACTITIONER	
		☐ OCCUPATIONAL THERAPIST	
		☐ OPHTHALMOLOGIST	
		☐ ORTHOPEDIC SURGEON	
		☐ OPTOMETRIST	
		☐ PHYSIATRIST	
		☐ PHYSICAL THERAPIST	
		☐ PLASTIC SURGEON	
		☐ PODIATRIST	
		☐ PSYCHOLOGIST	
		☐ PULMONOLOGIST	
		☐ RADIOLOGIST	
		☐ REPRODUCTIVE ENDOCRINOLOGIST	
		☐ RHEUMATOLOGIST	

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
		☐ SURGEON	
		☐ UROLOGIST	
		☐ UNKNOWN	
		☐ OTHER HEALTH CARE PRACTITIONER (specify type):	
☐ Urgent Care		☐ AUDIOLOGIST	
		☐ ALLERGIST	
		☐ CARDIOLOGIST	
		☐ DENTIST	
		☐ DERMATOLOGIST	
		☐ ENDOCRINOLOGIST	
		☐ ENT	
		☐ FAMILY PHYSICIAN	
		☐ GASTROENTEROLOGIST	
		☐ GYNECOLOGIST	
		☐ HEMATOLOGIST	
		☐ HEPATOLOGIST	
		☐ IMMUNOLOGIST	

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
		☐ INFECTIOUS DISEASE SPECIALIST	
		☐ INTERNAL MEDICINE SPECIALIST	
		☐ INTERNIST	
		☐ MEDICAL GENETICIST	
		☐ NEPHROLOGIST	
		☐ NEUROSURGEON	
		☐ NURSE	
		☐ NURSE PRACTITIONER	
		☐ OCCUPATIONAL THERAPIST	
		☐ OPHTHALMOLOGIST	
		☐ ORTHOPEDIC SURGEON	
		☐ OPTOMETRIST	
		☐ PHYSIATRIST	
		☐ PHYSICAL THERAPIST	
		☐ PLASTIC SURGEON	
		☐ PODIATRIST	
		☐ PSYCHOLOGIST	
		☐ PULMONOLOGIST	

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
		☐ RADIOLOGIST	
		☐ REPRODUCTIVE ENDOCRINOLOGIST	
		☐ RHEUMATOLOGIST	
		☐ SURGEON	
		☐ UROLOGIST	
		☐ UNKNOWN	
		☐ OTHER HEALTH CARE PRACTITIONER (specify type):	
☐ Emergency Room		☐ AUDIOLOGIST	
		☐ ALLERGIST	
		☐ CARDIOLOGIST	
		☐ DENTIST	
		☐ DERMATOLOGIST	
		☐ ENDOCRINOLOGIST	
		☐ ENT	
		☐ FAMILY PHYSICIAN	
		☐ GASTROENTEROLOGIST	
		☐ GYNECOLOGIST	

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
		☐ HEMATOLOGIST	
		☐ HEPATOLOGIST	
		☐ IMMUNOLOGIST	
		☐ INFECTIOUS DISEASE SPECIALIST	
		☐ INTERNAL MEDICINE SPECIALIST	
		☐ INTERNIST	
		☐ MEDICAL GENETICIST	
		☐ NEPHROLOGIST	
		☐ NEUROSURGEON	
		☐ NURSE	
		☐ NURSE PRACTITIONER	
		☐ OCCUPATIONAL THERAPIST	
		☐ OPHTHALMOLOGIST	
		☐ ORTHOPEDIC SURGEON	
		☐ OPTOMETRIST	
		☐ PHYSIATRIST	
		☐ PHYSICAL THERAPIST	
		☐ PLASTIC SURGEON	

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only			
2. What type of facility was the subject seen at?	**3. How many times was the subject seen by each facility?**	**4. What type(s) of *Non-Study* Health Care Practitioner was the Subject seen by? (Check all that apply)**	**5. How many times was the subject seen by each *Non-Study* Health Care Practitioner?**
		☐ PODIATRIST	
		☐ PSYCHOLOGIST	
		☐ PULMONOLOGIST	
		☐ RADIOLOGIST	
		☐ REPRODUCTIVE ENDOCRINOLOGIST	
		☐ RHEUMATOLOGIST	
		☐ SURGEON	
		☐ UROLOGIST	
		☐ UNKNOWN	
		☐ OTHER HEALTH CARE PRACTITIONER (specify type):	
6. Did the Subject have any diagnostic or therapeutic procedures performed since the last scheduled monthly study visit? ☐ No ☐ Yes **(If Yes, complete questions 7 and 8 below)**			

Record Non-Adverse Event Related Visits Below Any Visits Associated with Adverse Events should be Recorded on the Adverse Event eCRF only		
7. Diagnostic/Therapeutic Procedure (Check all that apply)	**8. How many times was the procedure performed?**	
Ultrasound Scan	☐	
Physical Examination	☐	
Vital Signs	☐	
MRI	☐	
CT Scan	☐	
X-Ray	☐	
Biopsy and Histologic Examination	☐	
Pelvic Exam	☐	
Urine Test	☐	
Blood Test	☐	
Other (specify):_____	☐	

Appendix M. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Global Protocol Change

"Estradiol 1.0 mg" has been changed to read "Estradiol 1 mg" throughout the protocol.

Specific Protocol Changes

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Efficacy:"
Sub-heading "Secondary Efficacy Variables:" previously read:

Secondary Efficacy Variables:

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

Has been changed to read:

Secondary Efficacy Variables:

- MBL volume assessed using alkaline hematin methodology and UBQ
- Suppression of bleeding
- Hemoglobin concentration

Other Efficacy Variables:

- Amenorrhea
- Control of bleeding
- Bleeding days
- Fibroid and uterine volume
- UFS-QoL Questionnaire
- EuroQol (EQ-5D-5L) Questionnaire
- Health Care Resource Utilization (HCRU) Questionnaire

- Patient Global Impression of Change (PGIC) Questionnaires
- Work Productivity and Activity Impairment (WPAI) Questionnaire

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Primary Efficacy Analysis:"
First paragraph previously read:

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

Has been changed to read:

The primary analysis of the primary endpoint will be performed using the full analysis set, which is comprised of all subjects who took at least one dose of the study drug in this Extension Study.

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Analyses for Secondary Efficacy Variables:"
Heading previously read:

Analyses for Secondary Efficacy Variables:

Has been changed to read:

Analyses for Secondary and Other Efficacy Variables:

Section 5.1 Overall Study Design and Plan: Description
Subsection Visit Window
First paragraph, second sentence previously read:

Each subsequent monthly visit should be scheduled based on the date of the Day 1 Visit.

Has been changed to read:

During the Treatment Period, each subsequent monthly visit should be scheduled based on the date of the Day 1 Visit.

Table 1. Visit and Assessment Windows
"Post-Treatment Follow-Up Period," second row previously read:

Month 6: MRI (if participating in MRI subset),Ultrasound, DXA Scan	–15 or +4 days

Has been changed to read:

Month 6: Ultrasound, DXA Scan	–15 or +4 days

Section 5.3.1.1 Study Procedures
Subsection <u>Pap Test</u>
First paragraph previously read:

A Pap test will be performed at Treatment Period Month 6 or Premature Discontinuation Visit (only performed if subject discontinues at or after the Post-Treatment Follow-Up Period Month Visit).

Has been changed to read:

A Pap test will be performed at Treatment Period Month 6 or Premature Discontinuation Visit.

Section 5.3.1.1 Study Procedures
Subsection <u>Endometrial Biopsy</u>
Delete: sixth paragraph

In the event the Month 6 biopsy cannot be performed at Month 6 or the Premature Discontinuation Visit (e.g., due to a stenotic cervix or location of fibroids), or an insufficient biopsy sample is obtained and the concurrent TVU indicates a thickness of > 4 mm, a repeat biopsy must be performed. If upon repeat, a sample cannot be obtained or remains insufficient, the AbbVie TA MD should be consulted.

Section 5.3.1.1 Study Procedures
Subsection Mammogram
Previously read:

All subjects who had a mammogram performed to determine eligibility into their respective Pivotal Study will have a mammogram performed at Treatment Period Month 6.

Has been changed to read:

All subjects who had a mammogram performed to determine eligibility into their respective Pivotal Study, will have a mammogram performed at Treatment Period Month 6 or at the Premature Discontinuation Visit if it has been approximately 12 months since the screening mammogram was performed.

Table 3. Clinical Laboratory Tests
Delete: column "Serology Testing"

Serology Testing
HAV-IgM
HbsAg
HCV Ab
HIV Ab

Section 5.3.3.2 Secondary Efficacy Variable
Delete: last bullet

Fibroid and uterine volume

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

The subject requires surgical intervention for treatment of uterine fibroids and menstrual bleeding or other procedures including hysterectomy, myomectomy, uterine artery embolization, high intensity focused ultrasound (HIFU), endometrial ablation, dilation and curettage (D&C), etc.

Has been changed to read:

The subject requires surgical intervention for treatment of uterine fibroids and menstrual bleeding or other procedures including hysterectomy, myomectomy, uterine artery embolization, high intensity focused ultrasound (HIFU), endometrial ablation, dilation and curettage (D&C), etc. during the Treatment Period. In the post treatment period these procedures do not warrant withdrawal if performed during the Post-Treatment Period unless a hysterectomy with bilateral salpingo-oophorectomy (BSO) is performed and the Subject does not plan to use Hormone Replacement Therapy within 1 month of the surgery date.

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

The subject has ALT or AST elevation > 5 times the upper limit of normal confirmed upon repeat.

Has been changed to read:

The subject has ALT or AST elevation > 5 times the upper limit of normal confirmed upon repeat during the Treatment Period.

Section 5.4.1 Discontinuation of Individual Subjects
First paragraph
Add: new last sentence

Each subsequent monthly Post-Treatment Follow-Up Period Visit should be scheduled based on the date of the last dose of study drug.

Section 5.5.5 Blinding of Investigational Product
Last paragraph
Add: new last sentence

AbbVie will remain blinded until the database of the 6-month Treatment Period is locked.

Section 8.1.2 Data Sets Analyzed
Subsection Modified Intent-to-Treat (mITT) Analysis Set
Subsection title and text previously read:

Modified Intent-to-Treat (mITT) Analysis Set

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

Has been changed to read:

Full Analysis Set

The full analysis set is comprised of all subjects who took at least one dose of the study drug in this Extension Study. The full analysis set will be used for all efficacy analyses unless otherwise specified in the Statistical Analysis Plan (SAP).

Section 8.1.7.1.1 Primary Analysis
Second paragraph previously read:

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

Has been changed to read:

The primary analysis of the primary endpoint will be performed using the full analysis set which is comprised of all subjects who took at least one dose of the study drug in this Extension Study.

Section 8.1.7.1.2 Derivation of Primary Efficacy Endpoint
First bullet, first sentence previously read:

If a subject has any AH data reported during the Final Month (i.e., she has at least 1 day of AH data during the last 28 days of treatment), then her primary endpoint will be based on AH data during the Final Month.

Has been changed to read:

If a subject has any evaluable AH data reported during the Final Month (i.e., she has at least 1 day of AH data during the last 28 days of treatment), then her primary endpoint will be based on AH data during the Final Month.

Section 8.1.7.1.3 Multiple Imputation
Last paragraph, last sentence previously read:

And the percentages of responders are analyzed using a logistic regression model including treatment as the main effect and baseline MBL volume as a covariate.

Has been changed to read:

The percentage of responders will be summarized by treatment group.

Section 8.1.7.1.4 Sensitivity Analysis of the Primary Efficacy Variable
Last paragraph previously read:

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

Has been changed to read:

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

Section 8.1.7.2 Secondary Efficacy Variables
Previously read:

The secondary efficacy measures during the Treatment Period of the Extension Study include the following:

- Change and percent change from baseline in MBL volume to each month and to the Final Month;
- Percentage of subjects with suppression of bleeding (no bleeding allowed, spotting allowed) at the Final Month;
- Percentage of subjects with baseline hemoglobin ≤ 10.5 g/dL who have an increase in hemoglobin > 2 g/dL at Month 6;
- Percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline during 28-day intervals throughout the Treatment Period;
- Change from baseline in total number of sanitary products used;
- Change and percent change from baseline in hemoglobin concentration;
- PGIC for Menstrual Bleeding and Non-Bleeding Uterine Fibroid Symptoms;
- Change and percent change from baseline in fibroid and uterine volume;
- Change from baseline for the UFS-QoL;
- Change from baseline for the EuroQoL-5D (EQ-5D-5L);
- The HCRU;
- Change from baseline for the WPAI.

Analysis details will be specified in the SAP.

Has been changed to read:

The secondary efficacy measures during the Treatment Period of the Extension Study include the following:

- Change and percent change from baseline in MBL volume to each month and to the Final Month;

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

8.1.7.3 Other Efficacy Variables

- Percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from baseline during 28-day intervals throughout the Treatment Period;
- Percentage of subjects with amenorrhea;
- Percentage of subjects with control of bleeding;
- The bleeding days;
- Change and percent change from baseline in hemoglobin concentration;
- PGIC for Menstrual Bleeding and Non-Bleeding Uterine Fibroid Symptoms;
- Change and percent change from baseline in fibroid and uterine volume;
- Change from baseline for the UFS-QoL;
- Change from baseline for the EuroQoL-5D (EQ-5D-5L);
- The HCRU;
- Change from baseline for the WPAI.

Analysis details will be specified in the SAP.

Section 8.1.7.2.1 Reduction of Bleeding
Last paragraph
Delete: last sentence

In addition, the change from baseline in total number of sanitary products will be summarized by treatment group.

Section 8.1.8.4 Bone Mineral Density
Last paragraph previously read:

The number and percentage of subjects with categorized percent change from baseline to Month 6 in the Extension Study in BMD (e.g., ≤ –3%, ≤ –5%, or ≤ –8%) will be summarized for each treatment group. Analysis details will be specified in the SAP.

Has been changed to read:

The number and percentage of subjects with categorized percent change from baseline to Month 6 in the Extension Study in BMD (≤ 0%, > 0% – ≤ 1.5%, > 1.5% – ≤ 3%, > 3% – ≤ 5%, > 5% – < 8%, or ≥ 8%) will be summarized for each treatment group. Analysis details will be specified in the SAP.

Section 8.2 Determination of Sample Size
Delete: first sentence

All subjects who complete either Pivotal Study M12-815 or Study M12-817, sign an inform consent form, and meet eligibility will be eligible to enroll in this Extension Study.

Appendix B. List of Protocol Signatories
Previously read:

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

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Development
		Global Drug Supply Management
		Clinical Operations
		Clinical Pharmacokinetics
		Bioanalysis
		Clinical Development
		Data and Statistical Sciences

Appendix C. Study Activities – Treatment Period and Post-Treatment Follow-Up Period
Subsection Treatment Period
Procedure "Clinical Safety Labs: Chemistry, Lipid Panel and Hematology," "Urine Pregnancy Tests," and "Contraception Counseling/Dispense Contraceptives as Necessary" previously read:

Procedure	Treatment Period[a]									
	Day 1[b]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[c]	Unsch Visit	PD (if appl)
Clinical Safety Labs: Chemistry, Lipid Panel and Hematology		X	X	X	X	X	X	X		X
Urine Pregnancy Tests	X[o]	X[p,q]	X[p,q]	X[p,q]	X[p,q]	X[p,q]	X[q]		X	X
Contraception Counseling/Dispense Contraceptives as Necessary	X[r]	X	X	X	X	X	X			X

Has been changed to read:

Procedure	Treatment Period[a]									
	Day 1[b]	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	PCV[c]	Unsch Visit	PD (if appl)
Clinical Safety Labs: Chemistry, Lipid Panel and Hematology		X	X	X	X	X	X			X
Urine Pregnancy Tests	X[o]	X[p,q]	X[p,q]	X[p,q]	X[p,q]	X[p,q]	X[q]	X		X
Contraception Counseling/Dispense Contraceptives as Necessary	X[r]	X	X	X	X	X	X	X		X

Appendix C. Study Activities – Treatment Period and Post-Treatment Follow-Up Period
Subsection Treatment Period
Table note "g." previously read:

All subjects who had a Mammogram in the Pivotal Study will have a mammogram performed at the Month 6 or Premature Discontinuation Visit of this Extension Study.

Has been changed to read:

All subjects who had a Mammogram in the Pivotal Study will have a mammogram performed at Month 6 or at the Premature Discontinuation Visit if it has been approximately 12 months since the screening mammogram was performed.