2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Elagolix (ABT-620)		
Name of Active Ingredient: Elagolix		

Title of Study: Extension Study to Evaluate the Long-Term Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain

Coordinating Investigator: [redacted] MD

Study Sites: 131 sites in the United States, Puerto Rico, and Canada

Publications: none

Studied Period (Years): First Subject First Visit: 28 December 2012 Last Subject Last Visit: 15 April 2016	**Phase of Development:** 3

Objectives:

The primary objective of this 6-month extension study was to evaluate the continued safety and tolerability of the 150 mg once daily (QD) and 200 mg twice daily (BID) doses of elagolix for up to 12 months (initial 6 months if on active treatment in pivotal Study M12-665 and an additional 6 months in this extension study) in the management of moderate to severe endometriosis-associated pain.

The efficacy endpoints included the proportion of responders based upon the mutually exclusive scales for daily assessment of dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP) measured by the Daily Assessment of Endometriosis Pain (by the daily electronic 4-point pain impact scale, which was developed according to the Food and Drug Administration (FDA) criteria for patient-reported outcomes, based in in part, on the Biberoglu and Behrman [B&B] scale). Use of analgesic medication for endometriosis-associated pain was included in the responder definition. The secondary efficacy objectives were assessed using the electronic daily diary (e-Diary) and questionnaires.

Methodology:

Study M12-667 was a Phase 3, multicenter, double-blind, randomized extension study evaluating the safety and efficacy of long-term treatment with 2 doses of elagolix (150 mg QD and 200 mg BID) in the management of moderate to severe endometriosis-associated pain in adult premenopausal female subjects who participated in pivotal Study M12-665. All subjects who completed the 6-month Treatment Period in the pivotal study, met eligibility criteria, and provided informed consent entered the 6-month Treatment Period of this extension study. The study consisted of a 6-month Treatment Period; and a Post-Treatment Follow-up (PTFU) Period of up to 12 months.

Methodology (Continued):

Subjects on active treatment in the pivotal study who met all entry criteria continued to receive the same dose, either elagolix 150 mg QD (ELA/ELA 150 group) or elagolix 200 mg BID (ELA/ELA 200 group) for up to an additional 6 months in this extension study; subjects on placebo in the pivotal study were randomized to one of the 2 dose groups in a 1:1 ratio to receive either elagolix 150 mg QD (PBO/ELA 150 group) or elagolix 200 mg BID (PBO/ELA 200 group) for up to 6 months. Subjects in this extension study remained blinded to their original treatment from the pivotal study as well as their dose group in this extension study. Subjects continued to maintain a daily e-Diary and record DYS, NMPP, dyspareunia (DYSP), overall endometriosis-associated pain assessed with the numeric rating scale (NRS), menstrual period, uterine bleeding, and rescue analgesic medication use for endometriosis-associated pain. Study visits occurred at Day 1, Months 1, 2, 3, 4, 5, and 6/Premature Discontinuation. The specific drugs allowed for rescue analgesic use were the following: 1 nonsteroidal anti-inflammatory drug (NSAID) (naproxen 500 mg) or 1 narcotic (opioid) combination medication.

Following treatment, all subjects, except those who discontinued from the study because of pregnancy, were to enter the PTFU Period for up to 12 months (48 weeks). Subjects continued to use nonhormonal dual contraception and receive counseling on the importance of consistent use of appropriate and effective birth control through PTFU Month 6. After PTFU Month 3, subjects were permitted the use of hormonal contraception in place of nonhormonal dual contraception, if preferred. Pregnancy testing was performed monthly through PTFU Month 6.

During the first 6 months of the PTFU Period, subjects continued to record daily assessments of endometriosis-associated pain, menstrual period, analgesic use for endometriosis-associated pain, and uterine bleeding in the e-Diary. Prophylactic use of analgesics for endometriosis-associated pain continued to be prohibited through PTFU Month 6, although subjects were allowed the use of permitted analgesics on an "as needed" basis.

After completing a minimum of 6 months in the PTFU Period, a subject was considered to have completed the study if she had reported a post-treatment menses and demonstrated adequate bone recovery (≤ 1.5% bone loss in the spine and ≤ 2.5% bone loss in the total hip compared to pretreatment Baseline). All other subjects continued to return to the site at PTFU Month 9 and Month 12, and completed phone visits in months with no clinic visit, until return to menses and adequate bone recovery (if applicable) were demonstrated. Subjects who did not have acceptable bone mineral density (BMD) parameters at the end of the study (Month 12 of the PTFU Period) were to be referred to a bone specialist.

Number of Subjects (Planned and Analyzed): approximately 500 planned; 504 analyzed (149 ELA/ELA 150, 138 ELA/ELA 200, 108 PBO/ELA 150, and 109 PBO/ELA 200)

Diagnosis and Main Criteria for Inclusion:

Women who completed the 6-month Treatment Period in pivotal Study M12-665. At the start of Study M12-665, they were between 18 and 49 years of age, premenopausal with a clinical diagnosis of endometriosis established by documented surgical visualization within 10 years of study entry, and in otherwise good health. Subjects had switched from their usual analgesic rescue medication to only those permitted by the protocol and agreed to use 2 forms of nonhormonal contraception consistently during both the pivotal study and this extension study (through PTFU Month 6). The pivotal study required a 24- to 38-day menstrual cycle prior to entering the Screening Period and a Composite Pelvic Signs and Symptoms Score (CPSSS) total score of ≥ 6 at Screening with a score of at least 2 for DYS and at least 2 for NMPP. Requirements for entry into the pivotal study Treatment Period included ≥ 45 days of e-Diary entries and "moderate" or "severe" pain for DYS and NMPP using the Monthly Assessment of Endometriosis Pain on Day 1 (reflecting subject recall of the preceding menstrual month).

Exclusions criteria included clinically significant gynecological conditions observed on the pivotal study Month 6 transvaginal ultrasound (TVU), endometrial biopsy, or results from any other diagnostic procedures, and BMD loss ≥ 8% in the spine, femoral neck or total hip as specified per the algorithm for Management of Bone Loss at pivotal study Month 6.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Subjects received elagolix, either 150 mg QD or elagolix 200 mg BID, by mouth (PO). Each dose comprised the tablets shown in the following table.

		Tablet Administered			
Treatment		**Elagolix 150 mg**	**Placebo 150 mg**	**Elagolix 100 mg**	**Placebo 100 mg**
Elagolix 150 mg QD	Lot Number	12-001806	11-004854	11-005645	11-004851
	AM dose	1	0	0	2
	PM dose	0	0	0	2
Elagolix 200 mg BID	AM dose	0	1	2	0
	PM dose	0	0	2	0

Duration of Treatment: 6 months of elagolix treatment with a 6- to 12-month PTFU Period

Criteria for Evaluation

Efficacy: The coprimary efficacy endpoints were the proportion of responders at Month 6 based upon the mutually exclusive scales for daily assessment of DYS and NMPP measured by the Daily Assessment of Endometriosis Pain (pain impact scales); use of analgesic medication for endometriosis-associated pain was included in the responder definition.

Criteria for Evaluation (Continued)

Efficacy (Continued):

Secondary efficacy endpoints were the proportion of overall responders for DYS and NMPP at visits other than Month 6, as well as with the proportion of responders based only on pain scores and based only on analgesic use at each visit; proportion of responders at each month for DYSP, change from Baseline to each month in analgesic use to treat endometriosis related pain, and change from Baseline to each month in NRS scores for endometriosis-associated pain. Other secondary efficacy endpoints were response at each month to the Patient Global Impression of Change (PGIC) questionnaire, results of the Endometriosis Health Profile-30 (EHP-30) domain of pain and sexual relationship at each visit, summary of the Health Related Productivity Questionnaire (HRPQ) scores by visit, summary of endometriosis-related number of non-study health visits, and number of days in hospital and type of procedures performed based on the Health Resource Use Questionnaire (HRUQ).

Pharmacokinetic and Pharmacodynamic: Concentrations of elagolix were obtained during the 6-month Treatment Period. Concentrations of estradiol, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were obtained during the 6-month Treatment Period and through PTFU Month 3.

Safety: BMD was a key safety endpoint. Safety endpoints included adverse events (AEs) (including AEs of special interest), clinical safety laboratory parameters (including lipid profiles), and vital signs. Other safety assessments included pregnancy, uterine bleeding patterns, endometrial thickness, and ovarian cysts.

Statistical Methods

Efficacy:

The criterion for defining a subject as a responder for DYS, NMPP, and DYSP was the same as that used in the pivotal study, which was determined based on a receiver operating characteristics (ROC) analysis and also required no increased analgesic use for endometriosis-associated pain (generally a < 15% increase in average pill count of rescue analgesics). For DYS, NMPP, and DYSP, responses of "None," "Mild," "Moderate," and "Severe" were assigned a score of 0, 1, 2, and 3, respectively. The proportion of responders for DYS and NMPP was summarized for each month during the study, through Month 6 in the PTFU Period.

The average for efficacy parameters collected using the e-Diary (DYS, NMPP, DYSP, overall endometriosis-pain assessed with the NRS, and endometriosis-associated rescue analgesics) for each monthly time point except Month 1 was based on averaging over the 35 calendar days prior to and including the reference study day. For Month 1, average values were based on data collected between Study Day 2 and the Month 1 reference study day, not exceeding 35 days. If a subject's mean score for dysmenorrhea was undefined numerically for a time point because her daily e-Diary reports indicated that she did not experience her period on any days during the 35 calendar day time period, then mean score for DYS for that time point was set equal to zero (which reflects the absence of any dysmenorrhea during that reporting time period). The baseline pain score was defined as the average of the daily values reported during the last 35 calendar days prior to and including the first dose of elagolix, either in the pivotal study for subjects previously randomized to elagolix or in the extension study for subjects previously randomized to placebo.

Statistical Methods (Continued)

Efficacy (Continued):

The following sensitivity analyses for the proportion of DYS and NMPP overall responders at Month 6 were conducted: (1) The primary analysis was repeated using mixed-imputation. Subjects who discontinued because of AEs were considered nonresponders, and (2) The primary analysis was repeated with a modification of the criterion for increased analgesic use (If the increase in analgesic use within each class of rescue medication did not reflect an absolute increase of > 1 pill, the subject was not considered a nonresponder due to increased analgesic use). The sensitivity analyses were repeated where the responder/nonresponder categorization used percent change from Baseline in pain reduction and ROC thresholds from the pivotal study based on percent change from Baseline in the monthly average pain score and increased analgesic use (the same definition as before).

The mean change from Baseline to each month were summarized for each treatment group with mean, standard error, median, minimum and maximum for the following: DYS, NMPP, DYSP, overall endometriosis-pain assessed with the NRS, and percentage of days as well as the monthly average dose of endometriosis analgesic use for each analgesic category.

Summary statistics were also used for the following endpoints at each month by treatment group: number and percentage of subjects in each PGIC response category and the overall percentage of subjects with responses of "much improved" or "very much improved;" number and percentage of subjects in each EHP-30 domain of pain and sexual relationship, as well as the mean, standard deviation, median, minimum, and maximum for each of these domains; loss of productivity due to absenteeism and presenteeism, based on the data collected via the HRPQ, was summarized with the mean, standard deviation, median, minimum, and maximum; and endometriosis-related number of non-study–health visits, number of days in hospital, and type of medical procedures performed, based on the HRUQ.

Pharmacokinetics and Pharmacodynamics:

Plasma concentrations of elagolix and serum concentrations of hormones were listed for each subject by visit day and dose regimen. Elagolix plasma concentration data were summarized for each subject by binned time interval since last dose. Summary statistics of each hormone were determined at each study visit. The overall Month 1 to 6 median hormone value was calculated by taking the median of each subject's hormone value measured at each of her monthly study visits (study visits Months 1 to 6).

Safety:

All safety analyses were performed using observed data and summary statistics, by treatment group, and included the following safety assessments: AEs, laboratory and vital sign variables, and safety endpoints of BMD, electrocardiograms (ECGs), endometrial assessments, and pregnancy results. No statistical tests were applied.

Each AE was mapped to a Medical Dictionary for Regulatory Activities (MedDRA®) system organ class and preferred term according to the MedDRA AE coding dictionary. The number and percentage of subjects having treatment-emergent AEs (onset or worsened on or after the date of first dose through 30 days after the last dose of study drug) were summarized, including stratification of AEs by intensity and attribution to study drug, AEs of special interest (AESIs) defined by prespecified company MedDRA query (CMQ) categories and standardized MedDRA query (SMQ) categories, serious AEs (SAEs), deaths, and AEs resulting in discontinuation of study drug.

Statistical Methods (Continued)

Safety (Continued):

Clinical laboratory variables were summarized by mean change from Baseline to each visit, and by shift tables for changes from Baseline to minimum, maximum, and Final Visit in the Treatment Period. The mean percent changes in BMD from Baseline and the distribution of the categorical changes in BMD was summarized. Vital sign variables were analyzed for mean changes from Baseline. Subjects who met the criteria for potentially clinically significant laboratory, vital sign, weight, and BMD values were summarized.

The mean change in endometrial thickness (as measured by ultrasound), the number and percentage of subjects in the endometrial biopsy result categories, the number of uterine fibroids, and the number of subjects with clinically meaningful ovarian cyst findings were summarized. Bleeding patterns were characterized using the definitions formulated by the World Health Organization (WHO) based on 90 day reference periods and based on the subject's entries in the daily e-Diary, and the number of bleeding days, intensity, and the monthly and cumulative amenorrhea rate was summarized.

Non-treatment-emergent AEs, select laboratory parameters, and BMD changes were also assessed during the PTFU Period.

Summary/Conclusions

Efficacy in ELA/ELA Groups

Throughout the additional 6-months of elagolix treatment in this extension study, the treatment group that previously received elagolix in pivotal Study M12-665 maintained a response rate for DYS, NMPP, and DYSP similar to that was achieved during the pivotal study. Similarly, the mean decreases from Baseline in DYS, NMPP, DYSP, and overall endometriosis-associated pain score assessed with the NRS that were achieved by Month 6 of the pivotal study were maintained during the Treatment Period of this extension study.

The proportion of overall responders observed at Month 1 of Study M12-667 for DYS, NMPP, and DYSP was generally sustained over time through Month 6 during the Treatment Period in both the ELA/ELA 150 and the ELA/ELA 200 dose groups. Mean decreases in pain scores from Baseline to every visit were observed for DYS, NMPP, and DYSP. In both dose groups, a decrease in the mean number of days that subjects reported moderate or severe pain was observed as early as Month 1 for DYS, NMPP, and DYSP. Both dose groups experienced mean numerical decreases in any rescue analgesic use (average pill count, days of use). The results for these assessments are shown in the table below for Month 6 of the Treatment Period.

Summary/Conclusions (Continued)

Efficacy in ELA/ELA Groups (Continued)

DYS, NMPP, DYSP, Endometriosis-Associated Pain Assessed with NRS, and Rescue Analgesic Use at Month 6 During the Treatment Period in Study M12-667

Endpoint	ELA/ELA[a] 150 mg QD	ELA/ELA[a] 200 mg BID
Responders, n (%) of subjects		
DYS[a,b]	61 (52.1)	86 (78.2)
NMPP[a,b]	79 (67.5)	76 (69.1)
DYSP[a]	38 (45.2)	42 (60.0)
Mean change from Baseline		
DYS[a]	–1.02	–1.79
NMPP[a]	–0.75	–0.81
DYSP[a]	–0.49	–0.72
Endometriosis-associated pain assessed with NRS[c]	–2.58	–3.09
Change from Baseline in average daily rescue analgesic (NSAIDs or opioids) pill count[d]	–0.40	–0.56

a. ELA/ELA = Elagolix in pivotal Study M12-665; elagolix (same dosage) in this extension Study M12-667.
DYS and NMPP pain scale responses: none = 0, mild = 1, moderate = 2, and severe = 3.
DYSP pain scale responses: none = 0, mild = 1, moderate = 2, severe = 3, and "not applicable." Subjects who responded "not applicable" for the entire time point or at Baseline were excluded from the analysis.

b. Responder = pain reduction from Baseline (at least –0.81 for DYS, –0.36 for NMPP, –0.36 for DYSP) and no increased rescue analgesic use for endometriosis-associated pain.

c. Pain scale ranges from 0 (none) to 10 (worst pain ever).

d. Average pill count = total number of pills of rescue analgesic type ÷ length of window (usually 35 days).

Other Patient-Reported Outcomes

- PGIC: The mean PGIC value in each dose group was < 2.3 at every visit. There was a trend for lower mean scores in the 200 mg dose group (Month 6: 2.12 for ELA/ELA 150, 1.45 for ELA/ELA 200). The percentage of subjects who assessed their endometriosis-associated pain as "much improved" or "very much improved" at Month 6 was 69.4% for ELA/ELA 150 and 91.2% for ELA/ELA 200.
- EHP-30: Mean improvements were observed in in each of the 5 dimensions in both dose groups starting at Month 1 and persisting through Month 6, with greater improvements in the higher dose group.
- Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 6a: Improvements from Baseline were observed at every visit in both dose groups. The mean decreases from Baseline at Month 6 were –5.65 for ELA/ELA 150 and –8.00 for ELA/ELA 200.

Summary/Conclusions (Continued)

Other Patient-Reported Outcomes (Continued)

- HRPQ Hours of Work Lost in Workplace and Household: Mean improvements (decreases from Baseline) were observed at every visit for hours lost in the workplace due to absenteeism and due to presenteeism. The mean decreases from Baseline at Month 6 were –12.98 hours for ELA/ELA 150 and –15.15 hours for ELA/ELA 200 for hours lost in the workplace. Mean improvements were also observed for hours lost in the household due to absenteeism and due to presenteeism.

PTFU Pain Assessments

During the PTFU Period, the mean DYS, NMPP, DYSP, and overall endometriosis-associated pain score assessed with the NRS generally worsened from the final treatment value in all treatment groups. In general, there is no evidence to suggest durability of treatment effect after elagolix treatment is stopped.

The rescue analgesics (NSAID and/or opioid) use, assessed by mean average daily pill count, did not increase during the PTFU Period for the PBO/ELA 150 and ELA/ELA 150 groups, but small increases were observed for the PBO/ELA 200 and ELA/ELA 200 groups.

Efficacy in PBO/ELA Groups

The proportion of overall responders observed at Month 2 of Study M12-667 for DYS, NMPP, and DYSP was generally sustained over time through Month 6 during the Treatment Period in both the PBO/ELA 150 and the PBO/ELA 200 dose groups. Mean decreases in pain scores from Baseline to every visit were observed for DYS, NMPP, and DYSP. In both dose groups, a decrease in the mean number of days that subjects reported moderate or severe pain was observed as early as Month 1 for DYS, NMPP, and DYSP. Both dose groups experienced mean numerical decreases in any rescue analgesic use (average pill count, days of use). The results for these assessments are shown in the table below for Month 6 of the Treatment Period.

Summary/Conclusions (Continued)

Efficacy in ELA/ELA Groups (Continued)

DYS, NMPP, DYSP, Endometriosis-Associated Pain Assessed with NRS, and Rescue Analgesic Use at Month 6 During the Treatment Period in Study M12-667

Endpoint	PBO/ELA[a] 150 mg QD	PBO/ELA[a] 200 mg BID
Responders, n (%) of subjects		
DYS[a,b]	28 (32.6)	56 (64.4)
NMPP[a,b]	34 (39.5)	50 (57.5)
DYSP[a,b]	23 (39.0)	25 (43.1)
Mean change from Baseline		
DYS[a]	–0.60	–1.27
NMPP[a]	–0.39	–0.54
DYSP[a]	–0.37	–0.36
Endometriosis-associated pain assessed with NRS[c]	–1.52	–1.89
Change from Baseline in average daily rescue analgesic (NSAIDs or opioids) pill count[d]	–0.22	–0.38

a. PBO/ELA = Placebo in pivotal Study M12-665; elagolix in this extension Study M12-667.
DYS and NMPP pain scale responses: none = 0, mild = 1, moderate = 2, and severe = 3.
DYSP pain scale responses: none = 0, mild = 1, moderate = 2, severe = 3, and "not applicable." Subjects who responded "not applicable" for the entire time point at Baseline were excluded from the analysis.

b. Responder = pain reduction from Baseline (at least –0.81 for DYS, –0.36 for NMPP, –0.36 for DYSP) and no increased rescue analgesic use for endometriosis-associated pain.

c. Pain scale ranges from 0 (none) to 10 (worst pain ever).

d. Average pill count = total number of pills of rescue analgesic type ÷ length of window (usually 35 days).

Other Patient-Reported Outcomes

- PGIC: The mean PGIC value in each dose group was < 2.6 at every visit. There was a trend for lower mean scores in the 200 mg dose group (Month 6: 2.11 for PBO/ELA 150, 1.84 for PBO/ELA 200). The percentage of subjects who assessed their endometriosis-associated pain as "much improved" or "very much improved" at Month 6 was 70.4% for PBO/ELA 150 and 79.3% for PBO/ELA 200.
- EHP-30: Mean improvements were observed in each of the 5 dimensions in both dose groups, starting at Month 1 and persisting through Month 6
- PROMIS Fatigue Short Form 6a: Improvements from Baseline were observed at every visit in both dose groups. Mean decreases from Baseline at Month 6 were –3.92 for PBO/ELA 150 and –4.00 for PBO/ELA 200.

Summary/Conclusions (Continued)

Other Patient-Reported Outcomes

- HRPQ Hours of Work Lost in Workplace and Household: Mean improvements (decreases from Baseline) were observed at every visit during the Treatment Period of Study M12-667 for hours lost in the workplace due to absenteeism and due to presenteeism. The mean decreases at Month 6 for the total hours lost were –10.44 hours for PBO/ELA 150 and –13.03 hours for PBO/ELA 200 for hours lost in the workplace. Mean improvements were also observed for hours lost in the household due to absenteeism and due to presenteeism.

Pharmacokinetic and Pharmacodynamic Results:

Elagolix concentrations and effects on hormone suppression are overall consistent with data collected in healthy premenopausal women. The elagolix 200 mg BID dosing regimen appeared to have lower estradiol, LH, and FSH concentrations compared with the elagolix 150 mg QD dosing regimen.

Safety Results:

Overall, for both the ELA/ELA 150 and ELA/ELA 200 dose groups, the results of this extension study demonstrate a manageable safety profile for continued elagolix treatment up to a cumulative 12 months in the management of endometriosis-associated pain in premenopausal women. No new or unexpected safety findings were observed in this study and the most common AEs were consistent with hypoestrogenic effects (i.e., the mechanism of action of elagolix).

Treatment-emergent AEs occurred in the majority of subjects in this study: 74.5% ELA/ELA 150, 73.9% ELA/ELA 200, 73.1% PBO/ELA 150, and 75.2% PBO/ELA 200.

In subjects previously treated with elagolix in the pivotal study:

- The most common AEs in the ELA/ELA 150 group were urinary tract infection (11.4%), upper respiratory tract infection (10.7%), headache (6.7%), and sinusitis (6.7%). The most common AEs in the ELA/ELA 200 group were urinary tract infection (8.0%), nausea (7.2%), sinusitis (7.2%), and back pain (7.2%).
- AEs that the investigator considered reasonably possibly related to study drug were reported in 28.2% of subjects in the ELA/ELA 150 group, and 36.2% of subjects in the ELA/ELA 200 group. The most common reasonably possibly study-drug–related AE in both dose groups was hot flush (4.0% ELA/ELA 150, 5.1% ELA/ELA 200).
- The majority of AEs were mild or moderate in severity.
- AEs led to discontinuation in < 9% of subjects (4.0% ELA/ELA 150, and 8.7% ELA/ELA 200). The only AE that led to discontinuation in > 1 subject within a dose group was bone density decreased (6 subjects in the ELA/ELA 200 group).
- SAEs were reported in < 4% of subjects in each treatment group (3.4% ELA/ELA 150, 2.9% ELA/ELA 200). Most SAEs were reported by 1 subject each. Serious AEs led to study drug discontinuation in 3 subjects: 1 SAE of joint injury (ELA/ELA 150), 1 SAE of affective disorder (ELA/ELA 200), and 1 SAE of pelvic pain (ELA/ELA 200).

Summary/Conclusions (Continued)

Safety Results (Continued):

- Across both the pivotal Study M12-665 and extension Study M12-667, hot flush was the most common AESI. Most events of hot flush began within the first 2 months of elagolix treatment and the prevalence continued to be relatively stable throughout elagolix treatment. None of the events of hot flush that began in Study M12-667 was serious and none led to study drug interruption or discontinuation.

In subjects previously treated with placebo in the pivotal study:

- The most common AEs in the PBO/ELA 150 group were hot flush (16.7%), urinary tract infection (9.3%), and headache (9.3%). The most common AEs in the PBO/ELA 200 group were hot flush (30.3%), headache (13.8%), and nausea (11.0%).
- AEs that the investigator considered reasonably possibly related to study drug were reported in 38.0% of subject in the PBO/ELA 150 group and 51.4% of subjects in the PBO/ELA 200 group. The most common reasonably possibly study-drug related AE in both dose groups was hot flush (16.7% PBO/ELA 150, 29.4% PBO/ELA 200).
- The majority of AEs were mild or moderate in severity.
- AEs led to study drug discontinuation in < 11% of subjects (3.7% PBO/ELA 150, 10.1% PBO/ELA 200). AEs that led to discontinuation in > 1 subject within a dose group were hot flush (5 subjects in PBO/ELA 200 group) and mood swings (2 subjects in PBO/ELA 200 group).
- SAEs were reported in < 5% of subjects in each treatment group (4.6% PBO/ELA 150, 4.6% PBO/ELA 200). Most SAEs were reported by 1 subject each. Serious AEs led to study drug discontinuation in 2 subjects: 1 SAE of supraventricular tachycardia (PBO/ELA 150), and 1 SAE of pelvic pain (PBO/ELA 200).
- Hot flush was the most common AESI. Most events of hot flush began within the first 2 months of elagolix treatment and the prevalence continued to be relatively stable throughout elagolix treatment. None of the events of hot flush was serious, 1 led to study drug interruption (PBO/ELA 200), and 6 led to study drug discontinuation (1 PBO/ELA 150, 5 PBO/ELA 200).

No deaths were reported during the Treatment Period or the PTFU Period.

Laboratory Parameters, Vital Signs, and ECGs

Overall, administration of elagolix for an additional 6 months in the ELA/ELA groups and for 6 months in the PBO/ELA groups resulted in no clinically meaningful changes in laboratory parameters.

Elagolix treatment was associated with mean increases in lipids for low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and total cholesterol. The changes in total cholesterol, LDL-C, and HDL-C were not considered clinically important. Less than 1.5% of subjects had LDL-C values ≥ 190 mg/dL at Month 6 of the Treatment Period in this study, and no subject had LDL values that met this criterion at the PTFU final assessment. Increases in lipid parameters did not appear to be associated with increases in cardiovascular events.

Summary/Conclusions (Continued)

Safety Results (Continued):

- In subjects previously treated with elagolix in pivotal Study M12-665, the mean percent increases in the ELA/ELA 150 group were 5.30% for LDL-C, 5.11% for total cholesterol, 3.21% for HDL-C, and 25.29% for triglycerides. The mean percent increases in the ELA/ELA 200 group were 15.08% for LDL-C, 12.10% for total cholesterol, 7.12% for HDL-C, and 23.69% for triglycerides.
  - There appeared to be no further increases in cholesterol parameters with the continued additional 6-month elagolix treatment up to 12 months.
  - Less than 5% of subjects had LDL-C values that reached ≥ 190 mg/dL during the additional 6-month Treatment Period in this extension study with either elagolix dose.
- Overall changes in LDL-C/HDL-C ratios were small (< 0.25) due to the concomitant increase in HDL-C.
- The increases in cholesterol parameters were observed within the first 2 months and remained relatively stable thereafter. By PTFU Month 1, serum lipid values returned to baseline or near baseline levels.

There were no clinically significant mean changes in systolic or diastolic blood pressure or pulse rate during the study. No consistent clinically significant ECG findings were associated with elagolix treatment.

Bone Mineral Density

Categorical Percent Changes in BMD at the End of Treatment

The proportion of subjects with a BMD decrease > 5% at any anatomic location at Month 6 was as follows:

- In subjects previously treated with elagolix in pivotal Study M12-665, the proportion of the subjects with a BMD decrease > 5% at any location ranged from 3.5% to 14.1% in the ELA/ELA 150 group and from 24.3% to 38.9% in the ELA/ELA 200 group.
- In subjects previously treated with placebo in pivotal Study M12-665, the proportion of the subjects with a BMD decrease > 5% at any location ranged from 1.2% to 9.3% in the PBO/ELA 150 group and from 6.0% to 16.7% in the PBO/ELA 200 group.

More than 90% of subjects in each treatment group had a Z-score > –1 at Baseline, and in general, the proportion of subjects with Z-scores > –1 did not change for the 150 mg dose groups and slightly decreased in the 200 mg dose groups. Less than 4% of subjects in each treatment group had Z-scores ≤ –1.5 in any anatomic location after 12 months of elagolix treatment, and the greatest percentage of the subjects with Z-score < –1.5 was in the 200 mg BID group at the lumber spine location.

Mean BMD Changes During the Treatment Period

Elagolix treatment was associated with mean percent decreases from Baseline in BMD following 12 months of treatment with elagolix.

- In subjects previously treated with elagolix in pivotal Study M12-665, the mean percent decreases from Baseline at Month 6 were –0.63% for lumbar spine, –0.64% for total hip, and –0.71% for femoral neck in the ELA/ELA 150 group, and –3.61% for lumbar spine, –2.69% for total hip, and –2.60% for femoral neck in the ELA/ELA 200 group.

Summary/Conclusions (Continued)

Safety Results (Continued):

- In subjects previously treated with placebo in pivotal Study M12-665, the mean percent decreases from Baseline at Month 6 were –1.13% for lumbar spine, –0.33% for total hip, and –0.50% for femoral neck in the PBO/ELA 150 group, and –2.44% for lumbar spine, –1.59% for total hip, and –0.96% for femoral neck in the PBO/ELA 200 group.

BMD Changes During the PTFU Period

- The majority of subjects in the ELA/ELA groups with post-treatment BMD assessments showed BMD increases or no change from the BMD decreases observed at the end of treatment.
- In subjects with the greatest mean BMD decreases (ELA/ELA 200 group), the mean percent decreases from Baseline at PTFU Month 6 and PTFU Month 12 were progressively less than observed at the end of treatment at all 3 anatomic locations.

There appears to be no association between BMD decrease and increased incidence of bone fractures reported during the Treatment or the PTFU Periods for elagolix treatment.

No subject had a Z-score ≤ –2.0 at any time during the study.

Bleeding Patterns

In subjects previously treated with elagolix in pivotal Study M12-665, the most common uterine bleeding pattern during the last 90 days of treatment was no bleeding in the ELA/ELA 200 group (54.5% of subjects) and infrequent bleeding in the ELA/ELA 150 group (34.5% of subjects). Elagolix reduced the number of day of bleeding and spotting and bleeding intensity for the subjects who reported bleeding. Elagolix was not associated with prolonged and frequent bleeding. The percentage of subjects with amenorrhea was < 18% for ELA/ELA 150 and > 46% for ELA/ELA 200 at every time interval. Similar results were observed in PBO/ELA groups.

Among subjects who entered the PTFU Period, ≥ 90% of subjects in each treatment group reported a post-treatment menses within 2 months after stopping elagolix at both dosages in both the ELA/ELA and the PBO/ELA groups.

Endometrial Safety

The changes in endometrial thickness measured by TVU were minimal following elagolix treatment for up to 12 months (0.6 mm ELA/ELA 150, and –0.8 mm ELA/ELA 200, –0.2 mm PBO/ELA 150, –1.5 mm PBO/ELA 200).

There were no adverse endometrial findings in this study based on transvaginal ultrasound and biopsy assessments. A greater percentage of subjects had endometrial biopsy results of the normal quiescent or minimally stimulated category in the 200 mg dose groups versus the 150 mg dose groups at Month 6.

Summary/Conclusions (Continued)

Safety Results (Continued):

Ovarian Safety and Uterine Fibroids and Papanicolau (Pap) Results

Overall, few subjects had non-follicular ovarian cysts during the study. There were no consistent and clinically meaningful findings for ovarian safety or uterine fibroids following elagolix treatment for up to 12 months. Elagolix treatment was not associated with an increase in the number of subjects with ovarian cysts. No Pap result indicated high-grade squamous intraepithelial lesion (ASC-H) for any subject at the end of treatment.

Pregnancies

Thirteen pregnancies were reported during the Treatment Period (including up to 30 days after the last dose of study drug). Nine of the 13 pregnancies resulted in live births, 1 resulted in spontaneous abortions during the first trimester, and 2 were terminated by elective abortions. No congenital anomalies were reported.

The annualized pregnancy rates during the Treatment Period of this study were 8.08% for ELA/ELA 150, 0% for ELA/ELA 200, 6.64% for PBO/ELA 150, and 11.16% for PBO/ELA 200.

Conclusions:

The study conclusions for elagolix dosages of 150 mg QD and 200 mg BID for up to 12 months in the treatment of endometriosis-associated pain in are listed as follows:

- Both elagolix dosages demonstrated consistent and clinically relevant sustained improvement of the painful symptoms of endometriosis, including DYS, NMPP, and DYSP.
- Both elagolix dosages demonstrated consistent improvement in quality of life assessments.
- Consistent with its mechanism of action of suppressing estrogen levels, hypoestrogenic-related adverse effects, such as hot flush, increased lipid, and decreased BMD, were observed with elagolix treatment in this extension study. These events can be monitored, are reversible, and are manageable.
- Elagolix treatment was associated with BMD decreases. Once elagolix is discontinued and estradiol levels increased, BMD increases.
- Serum lipids increased following initiation of elagolix, then maintained stable levels during continued treatment. Lipids quickly returned to baseline levels upon cessation of elagolix.
- Elagolix reduced the number of days of bleeding and spotting as well as bleeding intensity. Elagolix induced amenorrhea that was sustained over the treatment period.
- No new or unexpected safety findings were observed in this extension study.
- Overall, the results from this extension study demonstrate favorable benefit/risk profiles for both 150 mg QD and 200 mg BID dosages of elagolix in the management of endometriosis with associated pain in premenopausal women. Elagolix represents an important new option for these women.