

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: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Elagolix in Subjects with Moderate to Severe Endometriosis-Associated Pain		
Coordinating Investigator: [REDACTED], MD, PhD		
Study Sites: 151 sites in the United States, Puerto Rico, and Canada		
Publications: 5 published abstracts and 1 journal article		
Studied Period (Years): First Subject First Visit: 22 May 2012 Last Subject Last Visit: 28 September 2015	Phase of Development: 3	
<p>Objectives:</p> <p>The primary objective of this study was to evaluate the safety, tolerability, and efficacy of elagolix (ABT-620), administered as 150 mg once daily (QD) or 200 mg twice daily (BID) for 3 months in the management of moderate to severe endometriosis-associated pain, and to evaluate the effect of elagolix treatment on analgesic use for endometriosis-associated pain. Secondary efficacy objectives included evaluation of persistence of efficacy at 6 months, and assessments of other endometriosis-related symptoms, analgesic use, as well as quality of life endpoints.</p>		
<p>Methodology:</p> <p>This was a Phase 3, multicenter, double-blind, placebo-controlled, randomized study to assess the safety and efficacy of 2 doses of elagolix (150 mg QD and 200 mg BID) versus placebo in premenopausal women 18 to 49 years of age with moderate to severe endometriosis-associated pain. The study consisted of 4 periods: 1) Washout Period (if applicable); 2) a Screening Period of up to 100 days prior to first dose; 3) a 6-month Treatment Period; and 4) a Post-Treatment Follow-up (PTFU) Period of up to 12 months (if applicable).</p> <p>Subjects with a diagnosis of endometriosis who were taking exclusionary hormonal contraceptives or hormonal therapy were to sign the informed consent and meet the applicable inclusion/exclusion criteria prior to initiating the Washout Period. Subjects who were not taking exclusionary medications that required washout were entered directly into the Screening Period. All subjects were to use 2 forms of nonhormonal contraception (nonhormonal dual contraception) and receive counseling on the importance of consistent, appropriate and effective use of birth control. An e-Diary was dispensed and training provided to record endometriosis-associated pain, numeric rating scale (NRS), menstrual period, uterine bleeding, and analgesic medication use for endometriosis-associated pain on a daily basis. At least 45 days of daily e-Diary entries were to be completed before a subject could enter into the Treatment Period.</p>		

Methodology (Continued):

Once eligibility was confirmed, subjects were enrolled into the Treatment Period, which was to occur between Days 1 to 10 of the onset (first day with full menstrual flow) of menses and were randomized to a treatment through an interactive response technology system. Subjects were randomized to 1 of 3 parallel dose groups in a 3:2:2 ratio to receive daily doses of either placebo, elagolix 150 mg QD, or elagolix 200 mg BID for 6 months. Since study drug was blinded and there was a BID dose group, all subjects were to self-administer study drug twice a day (in the morning and in the evening approximately 12 hours apart) under fasting conditions. Each subject was to continue taking study drug twice daily for up to 6 months. The Treatment Period (approximately 168 days) consisted of six 28-day months. Subjects continued to maintain a daily e-Diary and record endometriosis-associated pain (dysmenorrhea [DYS], nonmenstrual pelvic pain [NMPP], dyspareunia [DYSP]), menstrual period, uterine bleeding, NRS, rescue analgesic medication use for endometriosis-associated pain, and time of study medication dosing during the entire Treatment Period. 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.

Eligible subjects who completed the 6-month Treatment Period and consented to participate could enter a separate continuous-use extension study for 6 additional months of treatment with elagolix in which all subjects received active therapy. All activities for these subjects were outlined in a separate extension study protocol (Study M12-667). All other subjects, including subjects who prematurely discontinued from treatment, declined to participate in, or did not qualify for the extension study were to enter the PTFU Period within this study for up to 12 months. Subjects continued to use dual nonhormonal contraception and received counseling on the importance of consistent use of appropriate and effective birth control through Month 6 of the PTFU Period. After Month 3 in the PTFU Period, subjects began the use of hormonal contraception in place of dual nonhormonal contraception, if preferred. Pregnancy testing was performed through PTFU Month 6. During the first 6 months of the PTFU Period, subjects continued to record daily assessments of endometriosis-associated pain (DYS, NMPP, and DYSP) the NRS, rescue analgesic use for endometriosis-associated pain, menstrual period, and uterine bleeding in the e-Diary. Prophylactic use of analgesics for endometriosis-associated pain was prohibited through PTFU Month 6, although subjects were allowed to use 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 returned to menses and demonstrated adequate bone recovery ($\leq 1.5\%$ bone loss in the spine and $\leq 2.5\%$ bone loss in the total hip compared with pretreatment Baseline). All other subjects continued to return to the site at PTFU Months 9 and 12 (and completed phone visits in months with no clinic visit) until return to menses and adequate bone recovery (if applicable) had been 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):

875 planned; 872 randomized; 871 analyzed (randomized and received at least 1 dose of study drug).
Placebo: 375 planned, 374 randomized and analyzed; elagolix 150 mg QD 250 planned, 249 randomized and analyzed; elagolix 200 mg BID 250 planned, 249 randomized, 248 analyzed.

Diagnosis and Main Criteria for Inclusion:

Premenopausal women with a clinical diagnosis of endometriosis established by documented surgical visualization within 10 years of study entry in otherwise good health and who were between the ages of 18 and 49 years at the time they signed the informed consent were eligible for this study. Subjects agreed to switch from their usual analgesic rescue medication to only those permitted by the protocol and agreed to use 2 forms of nonhormonal contraception consistently. At Screening, subjects had a menstrual cycle with an interval of 24 to 38 days 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. To be eligible to enroll into the Treatment period, a subject had to have at least 45 days of e-Diary entries and had to have "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). Potential subjects with a history of previous nonresponse to gonadotropin releasing hormone (GnRH) agonists, GnRH antagonists, depot medroxyprogesterone acetate (DMPA), or aromatase inhibitors (i.e., no improvement in DYS or NMPP), subjects who required more than 2 weeks of continuous use of a prohibited long-acting narcotic or immediate-release narcotic for treatment of endometriosis-associated pain within 6 months of entry into the Washout Period (if applicable) or Screening Period, subjects who had chronic pelvic pain that was not caused by endometriosis or any other chronic pain syndrome (e.g., fibromyalgia, chronic back pain, myofascial pain syndrome, chronic headaches), which required chronic analgesic or other chronic therapy and which would interfere with the assessment of endometriosis-related pain, and subjects using any systemic steroids (e.g., oral or inhaled) for over 14 days within 3 months prior to Screening or who were likely to require treatment with systemic steroids during the course of the study were ineligible.

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

Orally administered tablets of elagolix 150 mg QD (lot number 11-004424) and elagolix 200 mg BID (lot numbers 11-004297 and 12-0001718).

Duration of Treatment:

6 months of treatment with a 6- to 12-month follow-up period for subjects who did not enroll into the extension study (Study M12-667).

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Orally administered tablets of placebo for elagolix 150 mg QD (lot number 11-004854) and placebo for elagolix 200 mg BID (lot numbers 11-004851 and 12-0005267).

Criteria for Evaluation

Efficacy:

The coprimary efficacy endpoints were the proportion of responders at Month 3 based upon the mutually exclusive scales for daily assessment of DYS and NMPP measured by the Daily Assessment of Endometriosis Pain (by the daily electronic 4-point pain impact scale, which was developed according to the FDA criteria for patient-reported outcomes, based in part, on the Biberoglu and Behrman [B&B] scale); use of analgesic medication for endometriosis-associated pain was included in the responder definition.

Ranked secondary efficacy variables assessed (in the order of the variables tested) were as follows:

1. Change from Baseline to Month 3 in NRS;
2. Change from Baseline to Month 6 in DYS.
3. Change from Baseline to Month 6 in NMPP.
4. Change from Baseline to Month 3 in analgesic use across both classes of rescue analgesics based on pill counts.
5. Change from Baseline to Month 6 in analgesic use across both classes of rescue analgesics based on pill counts.
6. Change from Baseline to Month 3 in DYSP.
7. Change from Baseline to Month 3 in use of opioid class of medication based on pill counts.

Additional nonranked secondary efficacy variables included the following:

- Proportion of responders for DYS and NMPP at time points other than Month 3.
- Proportion of responders for DYSP at each month.
- Change from Baseline to each month in the mean pain score for DYS, NMPP, DYSP, and NRS as assessed by the e-Diary.
- Change from Baseline to each month in analgesic use across both classes of rescue analgesics, as assessed by the e-Diary.
- Response at each month in the Patient Global Impression of Change (PGIC) questionnaire.
- Change from Baseline to each scheduled assessment in the pain domain and sexual relationship domain of EHP-30 questionnaire scores.
- Change from Baseline to each scheduled assessment in Health Related Productivity Questionnaire scores.
- Endometriosis-related number of non-study-related health visits, number of days in hospital and type of procedures performed based on Health Resource Use Questionnaire

Pharmacodynamic:

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

Safety:

BMD was a key safety endpoint. Safety endpoints included adverse events (AEs) (including adverse events 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:

Coprimary Endpoints

Each elagolix dose group needed to demonstrate a statistically significantly greater proportion of responders for DYS and responders for NMPP in order for the dose group to be considered more efficacious than placebo for the primary endpoint. To maintain the overall type I error rate, the Bonferroni method was used to adjust for multiple comparisons (multiple elagolix dose groups).

For each of the coprimary endpoints, the criterion for defining a subject as a responder at Month 3 included a reduction of X or greater from Baseline in pain where X was determined based on a receiver operating characteristics (ROC) analysis described below, as well as no increased rescue analgesic use for endometriosis-associated pain.

The subjects recorded use of rescue analgesic for endometriosis-associated pain daily in the e-Diary.

The definition of increased analgesic use was as follows:

- The average pill count of analgesics during the Screening Period was summarized over the last 35 days prior to and including the first dose of study medication.
- For the coprimary endpoints of DYS and NMPP, subjects were considered nonresponders if they had an increase (generally 15% or greater) from Baseline in average pill count of rescue analgesics.

The average for efficacy parameters collected using the e-Diary (DYS, NMPP, DYSP, NRS) for each time was based on averaging over the 35 calendar days immediately prior to and including the reference study day, except for Month 1. For Month 1, average values were based on data collected between Study Day 2 and the Month 1 reference study day. If a subject's mean score for DYS was undefined numerically for a time point because her daily e-Diary reports indicated she did not experience her period on any days during the 35 calendar day time period, then the mean score for DYS for that time point was set equal to zero (absence of any DYS). The baseline pain score was defined as the average of the daily values reported during last 35 calendar days in the Screening Period prior to and including Day 1.

The analgesic use for any defined period was based on the average of the total pill count for each class of rescue analgesics (endometriosis-associated): NSAID and opioid. The total pill count for each class of rescue analgesic was the sum of the pill count of the corresponding class of rescue analgesic, as reported in the e-Diary during the time period of interest. For purposes of determining increased analgesic use, the averaging was done over the 35 calendar days preceding the time point of interest.

The coprimary efficacy endpoints were analyzed using a logistic regression model with the responder/nonresponder categorization as the dependent variable, treatment as the main effect, and baseline pain score as a covariate.

Statistical Methods (Continued)

Efficacy (Continued):

Coprimary Endpoints (Continued)

The following sensitivity analyses for the coprimary endpoint of proportion of responders at Month 3 were conducted for DYS and for NMPP:

- Using a chi-square test along with a 2-sided 97.5% confidence interval for the difference based on the normal approximation to the binomial distribution.
- Subjects who prematurely discontinued study drug at or before Month 3 were considered as nonresponders.
- Using mixed-imputation. Subjects who discontinued prior to or at Month 3 because of AEs were considered nonresponders.
- The criterion for increased analgesic use was modified so that subjects whose increase in analgesic use across each class of rescue medication did not reflect an absolute increase of more than 1 pill within each class of rescue analgesic were not considered nonresponders due to increased rescue analgesic use; overall responder status was determined only by pain response.

Secondary Endpoints

The ranked secondary analyses were evaluated with mixed-effects model with repeated measures (MMRM) analysis. The MMRM analysis includes change from baseline as the response, and the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, and the continuous fixed covariates of baseline score.

Nonranked secondary efficacy variables included assessments of the following endpoints at each postbaseline visit: DYS and NMPP, DYSP, analgesic use, and other patient-reported outcomes including PGIC, NRS, and EHP-30 domains of pain and sexual relationship.

The visit means for each of the pain parameters were summarized by visit. Change and percent change from baseline for each of the pain parameters was analyzed using a 1-way analysis of covariance (ANCOVA) model with baseline as a covariate and treatment as the main effect.

The percentage of subjects with various levels of pain relief (e.g., 10%, 20%, ..., 90% relative reduction in pain scores from baseline; or 0.1, 0.2, 0.3, etc., absolute reduction in pain scores from baseline) to each visit was summarized.

The mean change from Baseline to each visit in percentage of days as well as monthly average dose of rescue analgesic use for each analgesic category was summarized for each treatment group, and each elagolix dosing group was compared to the placebo group using a mixed-effect repeated measures method as well as a 1-way ANCOVA with treatment as the main factor and baseline as covariate.

The percentage of days a rescue analgesic for endometriosis-associated pain was taken by the subject was calculated for the following analgesic categories: NSAIDs or opioids, opioids only, NSAIDs only, and both NSAIDs and opioid analgesics.

The number and percentage of subjects in each PGIC response category were summarized at each postbaseline visit by treatment group, and statistical comparisons between each elagolix dosing group and the placebo group in mean scores at each postbaseline visit were performed using a 1-way analysis of variance (ANOVA).

Statistical Methods (Continued)

Efficacy (Continued):

Secondary Endpoints (Continued)

The number and percentage of subjects in each EHP-30 domain of pain and sexual relationship were summarized at each visit by treatment group. The results of EHP-30 domains of pain and sexual relationship were also summarized with the mean, standard deviation, and median for each treatment group. Comparisons were made between each elagolix dosing group and the placebo group using a 1-way ANCOVA with treatment as the main factor and baseline as a covariate.

Pharmacokinetics:

The plasma concentration data at all visits for each subject were summarized based on available times after the last dose recorded at each visit.

Pharmacodynamics:

Summary statistics of each hormone was 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:

Safety analyses included adverse events, laboratory parameters, vital sign parameters, and safety endpoints of BMD, electrocardiograms, endometrial safety, and pregnancy results. All safety analyses were based on observed data. Statistical comparisons were only performed between each elagolix dose group and placebo and during the Treatment Period.

Treatment-emergent adverse events were those that first occurred or worsened on or after the date of first dose of study drug through 30 days after the last dose of study drug. Each adverse event was mapped to a Medical Dictionary for Regulatory Activities (MedDRA[®]) system organ class and preferred term according to the MedDRA adverse event coding dictionary. Overall summaries of adverse event incidences, and stratification of adverse events by intensity and attribution to study drug were presented by treatment group. Adverse events of special interest defined by prespecified company MedDRA query (CMQ) categories and standardized MedDRA query (SMQ) categories were summarized by treatment group. Adverse events were also summarized for the PTFU Period.

For clinical laboratory variables changes from Baseline to each visit were compared between elagolix and placebo using contrast statements within a 1-way ANOVA, and shift tables for changes from Baseline to minimum, maximum, and Final Visit in the Treatment Period were provided. For lipids, changes from Baseline to each visit were compared between elagolix and placebo using contrast statements within a 1-way ANCOVA with baseline as a covariate, and shift tables for changes from Baseline to minimum, maximum, and Final Visit in the Treatment Period were provided. Subjects who met the criteria for potentially clinically significant laboratory values were summarized.

The mean percent changes in BMD from Baseline during the Treatment Period were compared between elagolix and placebo using a contrast within the 1-way ANOVA, and the distribution of the categorical changes in BMD was summarized. Z-scores and T-scores were also summarized.

For vital sign variables, analyses for the mean changes from Baseline were similar to those for clinical laboratory values. Subjects who met the criteria for potentially clinically significant vital sign and weight values were summarized and identified.

Statistical Methods (Continued)

Safety (Continued):

The mean change in endometrial thickness (as measured by ultrasound) and the number and percentage of subjects in the endometrial biopsy result categories were summarized. The number of uterine fibroids and the number of subjects with clinically meaningful ovarian cyst findings were also 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. The number of bleeding days and intensity were summarized by treatment group. The monthly and cumulative amenorrhea rate and post-treatment menstruation were summarized by treatment group. AEs, select laboratory parameters, and BMD changes were also assessed during the PTFU Period.

Summary/Conclusions

The mean age of the subjects enrolled was 31.5 years (ranging from 18 to 48 years). Most subjects (87.1%) were white, and 8.7% of the subjects were black or African American. Overall, 16.0% of subjects were of Hispanic or Latino ethnicity. Demographic characteristics were similar across all treatment groups.

Efficacy Results:

Among the 871 women who were randomized and treated in this study, 653 (75.0%) completed the study: 73% in the placebo group, 79% in the elagolix 150 mg QD group, and 74% in the elagolix 200 mg BID group. There was a dose-dependent and clinically meaningful effect for elagolix across all key efficacy endpoints.

Coprimary Efficacy Endpoints

Both elagolix treatment groups (150 mg QD and 200 mg BID) met the coprimary efficacy endpoints, with a statistically significantly greater proportion of responders for DYS and for NMPP at Month 3 compared with the placebo group. This effect was maintained for both elagolix doses relative to placebo at Month 6, demonstrating maintenance of effect.

- For DYS, responder rates were 46% at Month 3 and 42% at Month 6 for elagolix 150 mg QD and ~75% for elagolix 200 mg BID at Month 3 and Month 6, compared with placebo responder rates of 20% and 23%, respectively. Separation of effect from placebo was seen beginning at Month 1 for both elagolix dose groups.
- For NMPP, responder rates were 50% at Month 3 and 46% at Month 6 for elagolix 150 mg QD, and 55% and 62%, respectively, for elagolix 200 mg BID, compared with placebo response rates of 37% and 35%. Separation of effect from placebo was seen beginning at Month 1 for elagolix 200 mg BID and Month 2 for elagolix 150 mg QD.

Ranked Secondary Efficacy Endpoints

Elagolix 200 mg BID met all 7 ranked secondary endpoints. Elagolix 150 mg QD met the first 3 of the 7 ranked secondary endpoints.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Ranked Secondary Efficacy Endpoints (Continued)

Treatment Group	Visit N ^a	Baseline Mean	LS Mean (SE) Change	Difference in LS Mean Change (SE)	P value
1. Change from Baseline to Month 3 in NRS					
Placebo	329	5.58	-1.09 (0.098)		
Elagolix 150 mg QD	226	5.72	-1.74 (0.120)	-0.65 (0.155)	< 0.001
Elagolix 200 mg BID	213	5.48	-2.39 (0.122)	-1.30 (0.156)	< 0.001
2. Change from Baseline to Month 6 in DYS					
Placebo	288	2.17	-0.44 (0.047)		
Elagolix 150 mg QD	198	2.18	-0.89 (0.057)	-0.45 (0.074)	< 0.001
Elagolix 200 mg BID	182	2.19	-1.75 (0.059)	-1.32 (0.076)	< 0.001
3. Change from Baseline to Month 6 in NMPP					
Placebo	288	1.60	-0.31 (0.035)		
Elagolix 150 mg QD	198	1.64	-0.48 (0.043)	-0.16 (0.056)	0.004
Elagolix 200 mg BID	182	1.57	-0.72 (0.044)	-0.41 (0.057)	< 0.001
4. Change from Baseline to Month 3 in Analgesic Use Across Both Classes of Rescue Analgesics					
Placebo	329	0.87	-0.29 (0.032)		
Elagolix 150 mg QD	226	0.87	-0.29 (0.039)	-0.01 (0.051)	0.910
Elagolix 200 mg BID	213	0.85	-0.55 (0.040)	-0.26 (0.051)	< 0.001
5. Change from Baseline to Month 6 in Analgesic Use Across Both Classes of Rescue Analgesics					
Placebo	288	0.87	-0.27 (0.036)		
Elagolix 150 mg QD	198	0.87	-0.35 (0.043)	-0.07 (0.056)	0.185
Elagolix 200 mg BID	182	0.85	-0.56 (0.045)	-0.28 (0.057)	< 0.001
6. Change from Baseline to Month 3 in DYSP					
Placebo	246	1.51	-0.29 (0.041)		
Elagolix 150 mg QD	171	1.52	-0.39 (0.050)	-0.09 (0.065)	0.144
Elagolix 200 mg BID	153	1.55	-0.49 (0.052)	-0.20 (0.067)	0.003
7. Change from Baseline to Month 3 in Use of Opioids					
Placebo	329	0.37	-0.10 (0.024)		
Elagolix 150 mg QD	226	0.42	-0.07 (0.029)	0.03 (0.037)	0.424
Elagolix 200 mg BID	213	0.42	-0.22 (0.029)	-0.12 (0.038)	0.002

LS = least squares; SE = standard error

a. N is for the time point of interest for each analysis, not Baseline.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Nonranked Secondary Efficacy Endpoints

In analyses of mean changes in pain scores over time, elagolix resulted in dose-dependent clinically meaningful reductions in DYS, NMPP, and overall endometriosis-associated pain as assessed by the NRS. Both doses of elagolix resulted in reductions in DYS as early as Month 1 that were maintained through Month 6, and that were superior to placebo. Reductions in NMPP, which were superior to placebo, were observed as early as Month 1 with elagolix 200 mg BID and at Month 3 with elagolix 150 mg QD. With both doses, reductions in NMPP were superior to placebo from Month 3 throughout Month 6. For overall endometriosis-associated pain assessed by the NRS, reductions that were superior to placebo were observed beginning at Month 1 and were maintained through the 6 months of treatment for both doses.

Reductions in DYSP, which were superior to placebo, were observed with elagolix 200 mg BID as early as Month 3 and were maintained through Month 6. This effect was not observed with elagolix 150 mg QD. The improvements in DYSP scores were clinically meaningful, however, as demonstrated by a clinically meaningful change from Baseline at Months 3 and 6 at the group mean level, along with a reduced proportion of patients reporting days with moderate and severe pain at Month 3 and Month 6.

The percentage of overall responders for DYS was statistically significantly higher than placebo at every month beginning at Month 1 for both doses of elagolix. The percentage of overall responders for NMPP was statistically significantly higher than placebo at every month during the Treatment Period beginning at Month 2 with elagolix 150 mg QD and at every month beginning at Month 1 for elagolix 200 mg BID. The percentage of responders for DYSP was statistically significantly higher than placebo at Month 4 for elagolix 150 mg QD and at every month beginning at Month 2 for elagolix 200 mg BID.

In separate analyses of DYS, NMPP, and DYSP, for each elagolix treatment group, as early as Month 1, there was a decrease in the mean number of days subjects reported moderate and severe pain, and an increase in the mean number of days subjects reported no pain, with increasing levels of improvement in a dose-dependent manner at Month 6.

Reductions in pain were corroborated by clinically meaningful reductions in analgesic use. Both doses of elagolix resulted in numerical decreases in average pill count per day of any analgesic use in a dose-dependent fashion, with elagolix 200 mg BID reaching statistical significance compared with placebo at Month 3 and Month 6. Use of both classes of rescue analgesics declined by more than 40% with elagolix 150 mg QD and by more than 65% with elagolix 200 mg BID at the group mean level at Month 3, with an increasing proportion of subjects using no NSAIDs and/or no opioid analgesics at Month 3 and Month 6 representing clinically meaningful reductions in rescue analgesic use. Mean changes from Baseline in daily pill counts for any rescue analgesic use were -0.29 pills for elagolix 150 mg QD and -0.55 pills for elagolix 200 mg BID compared with -0.29 pills with placebo at Month 3; and -0.35 pills for elagolix 150 mg QD and -0.56 pills for elagolix 200 mg BID compared with -0.27 pills with placebo at Month 6. In addition, the median percentage of days when subjects reported any rescue analgesic use was smaller for each elagolix treatment groups relative to placebo, and this effect was dose-dependent.

A higher proportion of subjects in each elagolix treatment group than in the placebo group reported that their endometriosis-associated pain had "much improved" or "very much improved" beginning at Month 1 and persisting through 6 months of treatment on the PGIC questionnaire. Each of the elagolix treatment groups had a change in endometriosis-associated pain that was statistically significantly different ($P < 0.001$) from the placebo group beginning at Month 1 and persisting through 6 months of treatment.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Nonranked Secondary Efficacy Endpoints (Continued)

Improvements in other patient-reported outcomes, such as the EHP-30, which included 5 core dimensions (pain, control and powerlessness, emotional well-being, social support, and self-image) and 1 modular questionnaire (sexual intercourse), were also noted in a dose-dependent manner:

- A statistically significantly greater decrease from Baseline (improvement) compared with placebo was seen in 5 of the 6 dimension scores at Month 3 and in 4 of the 6 dimension scores at Month 6 for elagolix 150 mg QD and in all 6 dimension scores that comprise the EHP-30 for elagolix 200 mg BID. Superiority over placebo was seen as early as Month 1 for elagolix 200 mg BID in all 6 dimensions. The totality of EHP-30 data reflects an overall improvement of the quality of life among endometriosis patients treated with elagolix across multiple quality of life dimensions.

Similar improvements were seen in other patient-reported outcomes.

- Greater reductions were seen in the hours lost from the workplace and household due to absenteeism and presenteeism for both doses of elagolix compared with placebo at Month 3 and at Month 6.

Post-Treatment Pain Assessments

During the PTFU Period, the mean DYS, NMPP, DYSP, and NRS pain scores generally increased from the final treatment value for subjects who had received elagolix during the Treatment Period. No statistical tests were performed, and there was no consistent pattern in rescue analgesic use during the PTFU Period.

Efficacy Summary

In addition to the study's coprimary efficacy endpoints being met at Month 3, with maintenance of effect at Month 6, there were either numerical and/or statistically significant improvements for both elagolix doses compared with placebo for almost all key secondary endpoints evaluated, including improvements in quality of life measures. The clinical results of a dose-dependent increase in efficacy with elagolix 150 mg QD and 200 mg BID are consistent with the dose-dependent inhibition of estradiol with the 2 elagolix doses. Overall, the results of this pivotal study demonstrate clinically meaningful benefit with elagolix treatment in the management of endometriosis with associated pain in premenopausal women.

Pharmacokinetic Results:

The median trough concentration (C_{trough}) values were consistent with the concentration data collected in healthy premenopausal women in Phase 1 studies.

Pharmacodynamic Results:

A dose-dependent suppression of estradiol and LH was observed in both elagolix groups compared with placebo during the Treatment Period. For FSH, the elagolix 200 mg BID group appeared to have lower FSH concentrations compared with placebo, while the elagolix 150 mg QD group appears to have slightly higher FSH concentrations compared with placebo.

Summary/Conclusions (Continued)

Safety Results:

Adverse Events

The adverse event profile was consistent with the estrogen suppression mechanism of action of elagolix. Hypoestrogenic events were reported more frequently with elagolix treatment and in a dose-dependent manner. The majority of treatment-emergent AEs, including hot flush, were mild or moderate in intensity. The onset of hot flush generally occurred within 2 weeks after initiating treatment. Few AEs led to discontinuation of study drug. Hot flush was the most frequently reported AE leading to discontinuation in the elagolix treatment groups. However, discontinuation due to hot flush was low, with < 3% in the elagolix dose groups.

Few of the subjects who reported AEs of hot flush also reported night sweats. Overall, 15 of the 190 subjects who reported hot flush also reported night sweats at some point in the study, with a higher percentage of these in the elagolix 200 mg BID group. No elagolix-treated subject discontinued from study drug because of night sweats.

The rate of treatment-emergent serious AEs (SAEs) was low in this study and most preferred terms were reported for 1 subject each. SAEs led to study drug discontinuation for 5 subjects overall.

Serum Lipids

Elagolix also showed a dose-dependent effect on serum lipids that was also consistent with its mechanism of action. Both estrogens and androgens regulate the lipid biosynthesis in the liver. Elagolix resulted in increases in mean percent changes from Baseline in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, apolipoprotein B, and triglycerides that were statistically significantly different compared with placebo for most time points; increases occurred within 1 to 2 months after the start of elagolix therapy and remained relatively stable thereafter. The LDL-C increases with elagolix occur early in treatment, then stabilize, and are accompanied by concomitant increases in HDL-C, which minimize meaningful changes in lipid ratios, is worth noting. In addition, the proportions of subjects whose lipids values reached clinically significant levels are low. Increases in lipid parameters returned to baseline levels within 1 month after subjects stopped elagolix. The changes in total cholesterol, LDL-C, and HDL-C were not considered clinically important. Changes in lipids do not appear to be associated with increases in the incidence of cardiovascular events in this study.

Bone Mineral Density

Bone mineral density change was a key safety evaluation in this study because of estrogen suppression associated with the elagolix mechanism of action.

Elagolix showed a clear dose-dependent effect on the proportion of subjects who had BMD decrease > 5% while on treatment. Overall, after 6 months of treatment, the proportion of subjects with BMD decrease > 5% in any of the 3 anatomical locations was similar in the elagolix 150 mg QD group as in the placebo group, but the proportion was higher in the elagolix 200 mg BID group. A few subjects had BMD decrease \geq 8% during the study in the placebo and elagolix 150 mg QD groups, and more were in the elagolix 200 mg BID group.

Summary/Conclusions (Continued)

Safety Results (Continued):

Bone Mineral Density (Continued)

Both elagolix dose groups showed mean percent decreases in BMD compared with mean percent increases with placebo from Baseline to Month 6 in lumbar spine, total hip, and femoral neck in a dose-dependent manner. The magnitude of the effect on BMD with elagolix 150 mg QD was much smaller. The percent decrease from Baseline with elagolix 150 mg QD was < 0.4% in any of 3 anatomic locations. A small mean percent increase in lumbar spine BMD from Baseline was observed in placebo group.

Percent Change in BMD from Baseline to Month 6

Anatomic Location	Percent Change		
	Placebo	Difference from Placebo (95% CI)	
		Elagolix 150 mg QD	Elagolix 200 mg BID
Lumbar spine	+0.47	-0.32* -0.79 (-1.29, -0.30)	-2.61* -3.08 (-3.58, -2.59)
Total hip	+0.22	-0.32* -0.54 (-0.93, -0.15)	-1.52* -1.74 (-2.13, -1.35)
Femoral neck	+0.02	-0.39 -0.41 (-1.02, 0.20)	-1.89* -1.91 (-2.53, -1.29)

* Statistically significantly different from placebo.

More than 92% of subjects in each treatment group had a Z-score > -1 at Baseline, and ≥ 90% of subjects across all treatment groups remained at this Z-score level following the 6-month Treatment Period. A higher percentage of subjects in the elagolix 200 mg BID treatment group had a Z score that was ≤ -1.5 in the lumbar spine and femoral neck at Month 6 compared with placebo.

Although 167 subjects entered the PTFU Period, only a portion of subjects who had worse BMD decrease (i.e., decrease in BMD > 1.5% in lumbar spine and > 2.5% in total hip) were required to have follow-up BMD evaluations at PTFU Month 6. Similarly, although 90 subjects completed 6 months of the PTFU Period, only a portion were required to have follow-up BMD evaluations at PTFU Month 12 (those with decrease in BMD > 1.5% in lumbar spine or > 2.5% in total hip).

In the small number of subjects who had dual energy x-ray absorptiometry (DXA) scans at *both* Month 6 and PTFU Month 6 (n = 54), the mean percent increase in lumbar spine BMD was 0.79% for placebo, while the mean percent decrease was 1.28% for elagolix 150 mg QD, and 3.81% for elagolix 200 mg BID at PTFU Month 6. At PTFU Month 12, for the smaller number of subjects who had DXA scans at *both* Month 6 and PTFU Month 12 (n = 26), the mean percent increase in lumbar spine BMD was 1.94% for placebo, while the mean percent decrease was 4.00% for elagolix 150 mg QD and 3.88% for elagolix 200 mg BID.

No subject had a Z-score ≤ -2 in any anatomic location at any time point.

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

Summary/Conclusions (Continued)

Safety Results (Continued):

Uterine Bleeding, Endometrial Safety, and Transvaginal Ultrasound

Elagolix was associated with altered menstrual bleeding patterns compared with placebo. Elagolix also showed a dose-dependent reduction in the mean number of days of bleeding/spotting, a reduction in bleeding intensity, and a reduction in duration of bleeding in those subjects who reported bleeding. The majority of subjects reported a post-treatment menses within 1 month after stopping elagolix. The percentage of subjects with amenorrhea was higher than placebo with both elagolix doses at every time point. In an analysis of cumulative amenorrhea, the percentage of subjects with amenorrhea was also greater than placebo at every time point; at Month 6, the percentage of subjects with amenorrhea was 1.1% with placebo, 6.8% with elagolix 150 mg QD, and 27.8% with elagolix 200 mg BID. There were no adverse endometrial findings in this study based on transvaginal ultrasound and biopsy assessments. Elagolix treatment did not cause an increase in the frequency of ovarian cysts or uterine fibroids.

Pregnancy

Predefined nonhormonal contraceptives were required for each individual subject during Screening, the Treatment Period, and the first 3 months of the PTFU Period. There were 14 pregnancies reported during the Treatment Period (conception date within 30 days after the last dose of study drug): 8 in the placebo group, 4 in the elagolix 150 mg QD group, and 2 in the elagolix 200 mg BID group. The annualized pregnancy rates during this study were 5.05% for placebo, 3.72% for elagolix 150 mg QD, and 1.95% for elagolix 200 mg BID (2.86% for elagolix overall).

Conclusions:

The study met its coprimary efficacy endpoints, with each elagolix treatment group, 150 mg QD and 200 mg BID, showing a statistically significantly greater proportion of responders for DYS and for NMPP at Month 3 compared with the placebo group. This effect was maintained at Month 6, with a similarly statistically significantly greater proportion of responders for DYS and for NMPP in each elagolix treatment group compared with the placebo group.

Elagolix 150 mg QD treatment resulted in a statistically significant and clinically meaningful reduction in DYS and NMPP at Month 3 that continued over the 6-month duration of the study. The improvements in DYSP scores were clinically meaningful, as demonstrated by a clinically meaningful change from Baseline at Months 3 and 6 at the group mean level, along with a reduced proportion of patients reporting days with moderate and severe pain at Month 3 and Month 6. Use of both classes of rescue analgesics declined by more than 40% with elagolix 150 mg QD at the group mean level at Month 3, with an increasing proportion of subjects using no NSAIDs and/or no opioid analgesics at Month 3 and Month 6 representing clinically meaningful reductions in rescue analgesic use. Clinically important reductions in endometriosis-associated pain with the elagolix 150 mg dose were accompanied by clinically meaningful reductions in rescue analgesic use, including opioid rescue reductions.

Elagolix 200 mg BID met the coprimary endpoints as well as all 7 ranked secondary endpoints. Elagolix 200 mg BID demonstrated a robust effect across the coprimary (DYS and NMPP) and ranked secondary endpoints including DYSP, as well as a reduction in rescue analgesic use (both NSAIDs and opioids). Use of both classes of rescue analgesics declined by more than 65% with elagolix 200 mg BID at the group mean level, with an increasing proportion of subjects using no NSAIDs and/or no opioid analgesics at Month 3 and Month 6. Elagolix 200 mg BID also showed a clear trend of maintenance of efficacy after 3 months of treatment and up to 6 months.

Summary/Conclusions (Continued)

Conclusions (Continued):

The incidence of adverse events was generally similar across treatment groups, with exception of AEs leading to study drug discontinuation, and hot flush, both of which are dose-dependent and consistent with results from previous Phase 1 and Phase 2 studies. The majority of hot flush events were mild or moderate in intensity, and discontinuation rates due to hot flush were low. Treatment with elagolix for 6 months was associated with dose dependent decreases in BMD. The mean percent decreases from Baseline in BMD with elagolix 150 mg QD were small. However, higher mean percent decreases were observed with elagolix 200 mg BID, consistent with the higher estradiol suppression at this dose. Partial and progressive recovery was observed for BMD during the follow-up period. Importantly, no subject crossed the clinically important Z-score threshold of ≤ -2 in any anatomic location at any time point.

Treatment with elagolix for 6 months was associated with dose-dependent increases in serum lipid parameters consistent with its hypoestrogenic effect. These changes were observed early in the treatment and then stabilized. Serum lipids returned to baseline levels within 1 month after subjects stopped taking elagolix.

The results from this pivotal study showed that elagolix had a dose-dependent and clinically meaningful reduction in the painful symptoms associated with endometriosis. The results demonstrate that elagolix provides significant benefit with an acceptable safety profile in the management of endometriosis with associated pain in premenopausal women and represents an important new option for these women.