2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Elagolix (ABT-620)</td></tr>
<tr><td>Name of Active Ingredient:
Elagolix</td></tr>
<tr><td colspan="3">Title of Study: A Phase 2b Study to Evaluate the Safety and Efficacy of Elagolix in Premenopausal Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids</td></tr>
<tr><td colspan="3">Investigator: [redacted]</td></tr>
<tr><td colspan="3">Study Sites: 86 sites in the United States, United Kingdom, Chile, Canada, and Puerto Rico</td></tr>
<tr><td colspan="3">Publications: None</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 19 March 2013
Last Subject Last Visit: 08 December 2015</td><td>Phase of Development: Phase 2b</td></tr>
<tr><td colspan="3">Objectives:
• Assess the safety and efficacy of elagolix alone and in combination with 2 different strengths of add-back therapy (estradiol/norethindrone acetate [E2/NETA]) versus placebo to reduce heavy menstrual bleeding (HMB) (which is defined as > 80 mL blood loss per menstrual cycle) associated with uterine fibroids, and to reduce fibroid volume and uterine volume in premenopausal women 18 to 51 years of age, as well as to assess the impact of add-back therapy on uterine bleeding patterns.
• Assess the impact of add-back therapy E2/NETA (both strengths, E2 0.5 mg/NETA 0.1 mg or E2 1.0 mg/NETA 0.5 mg) on the efficacy, safety, and tolerability of elagolix, including hypoestrogenic side effects such as bone mineral density (BMD) changes (as assessed by dual energy x-ray absorptiometry [DXA]), and vasomotor symptoms such as hot flush.
• Evaluate the effects of elagolix (with and without add-back therapy) on nonbleeding uterine fibroid symptoms and quality of life (QoL) measures.</td></tr>
<tr><td colspan="3">Methodology:
This was a Phase 2b, randomized, double-blind, multicenter, placebo-controlled, 2-cohort dose-finding study to evaluate the efficacy and safety of 2 dosing regimens of elagolix (300 mg twice daily [BID] or 600 mg once daily [QD]) alone or in combination with 2 different strengths of hormonal add-back therapy (low-dose [LD] E2/NETA [E2 0.5 mg/NETA 0.1 mg] or standard-dose [SD] E2/NETA [E2 1.0 mg/NETA 0.5 mg]) versus placebo to reduce HMB associated with uterine fibroids in premenopausal women.</td></tr>
</table>

Methodology (Continued):

This study included a Screening, Treatment, and Post-Treatment Follow-up Period; subjects taking exclusionary medications entered into a Washout Period before entering the Screening Period.
During the two-and-a-half to three-and-a-half months Screening Period, subjects underwent screening procedures and assessments, used 2 forms of nonhormonal contraception (nonhormonal dual contraception), collected all sanitary products on days with menstrual bleeding or spotting over the course of 2 or 3 menstrual cycles, and recorded the presence and intensity of menstrual bleeding for each day and nonbleeding symptoms associated with uterine fibroids in an electronic diary (eDiary).
Once eligibility was confirmed, subjects were randomized to 1 of 4 parallel treatment groups in either Cohort 1 or Cohort 2 in the 6-month Treatment Period. Throughout the 6-month Treatment Period, subjects enrolled in Cohort 1 self-administered elagolix doses BID and E2/NETA doses QD, and subjects enrolled in Cohort 2 self-administered elagolix or E2/NETA doses QD. Subjects continued to use 2 forms of nonhormonal contraception and record the presence and intensity of menstrual bleeding in the daily eDiary throughout the Treatment Period. Subjects collected sanitary products from the Month 3 Visit through the Month 6 Visit of the Treatment Period for alkaline hematin analysis. All subjects, including those who prematurely discontinued from treatment, except those who discontinued due to pregnancy, were to enter the 6-month Post-Treatment Follow-Up Period. Continued use of nonhormonal dual contraception was required until Month 3 in the Post Treatment Follow-Up Period; thereafter, subjects were allowed to use hormonal contraception.

Number of Subjects Planned:

Approximately 520 subjects (260 subjects per cohort) were planned to be randomized in a 1:1:1:1 ratio of active to placebo to 1 of the 4 treatment arms per cohort. The number of subjects randomized and completed are outlined in the table below:

Cohort	Treatment	Randomized and Treated	Study Drug Completion
1	Placebo	65	50
	Elagolix 300 mg BID alone	65	52
	Elagolix 300 mg BID + LD E2/NETA QD	64	53
	Elagolix 300 mg BID + SD E2/NETA QD	65	52
2	Placebo	78	67
	Elagolix 600 mg QD alone	77	58
	Elagolix 600 mg QD + LD E2/NETA QD	76	53
	Elagolix 600 mg QD + SD E2/NETA QD	77	53

LD E2/NETA = estradiol 0.5 mg/norethindrone acetate 0.1 mg,

SD E2/NETA = estradiol 1.0 mg/norethindrone acetate 0.5 mg

Diagnosis and Main Criteria for Inclusion: Nonpregnant premenopausal women 18 to 51 years of age with HMB (menstrual blood loss [MBL] > 80 mL) and a diagnosis of uterine fibroids – at least 1 fibroid with a diameter ≥ 3 cm (longest diameter) or multiple small fibroids with a total uterine volume of ≥ 200 cm^3 to ≤ 2,500 cm^3; intramural, submucosal non-pedunculated, and large (≥ 4 cm) subserosal fibroids; or subserosal fibroids in combination with intramural and/or submucosal fibroids – who had a screening follicle-stimulating hormone (FSH) level of < 35 mIU/mL (35 IU/L), no evidence of cervical malignancy or premalignant changes, and no significant endometrial pathology, and who agreed to use dual contraception from Washout (if applicable) through Month 3 of the Post-Treatment Follow-Up Period were enrolled. Subjects were excluded if they had myomectomy, uterine artery embolization or high intensity focused ultrasound for fibroid destruction within 6 months prior to Screening or endometrial ablation within 5 years prior to Screening, oligomenorrhea, a clinically significant gynecological disorder (i.e., a persistent [more than 2 menstrual cycles] simple ovarian cyst > 5 cm in longest diameter, a complex ovarian cyst > 3.5 cm in longest diameter, or an endometrioma > 3.5 cm in longest diameter), intracavitary pedunculated submucosal fibroids (with or without an additional qualifying fibroid), solitary (other fibroids not present) pedunculated subserosal fibroids, and solitary small subserosal fibroids (less than 4 cm longest diameter), evidence of malignant or premalignant changes or a focal intracavitary lesion, and hemoglobin level < 6 g/dL.
Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number: Orally administered tablets of elagolix 150 mg, 600 mg total daily dose, 2 tablets BID or 4 tablets QD (lot numbers 12-001806, 12-004627, 13-000939, 13-002192, 13-002317) Orally administered over-encapsulated tablets of LD E2/NETA (0.5 mg/0.1 mg), 1 capsule QD (lot numbers, 14-004517, 13-002658, 13-003632, 14-001808) Orally administered over-encapsulated tablets of SD E2/NETA (1.0 mg/0.5 mg), 1 capsule QD (lot numbers 14-004008, 14-006397, 13-002676, 13-003633, 14-001690, 15-000086) **Duration of Treatment:** 6 months of treatment
Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number: Orally administered tablets of placebo for elagolix 150 mg, 2 tablets BID or 4 tablets QD (lot number 12-005258, 13-006146) Orally administered placebo capsules for LD and SD E2/NETA, 1 capsule QD (lot numbers 12-004118, 14-001216)

Criteria for Evaluation

Efficacy:

Primary Efficacy Endpoint:

The primary endpoint was the percentage of subjects meeting a composite endpoint consisting of these 2 bleeding assessments:

- MBL volume of < 80 mL at the Final Month (last 28 days of treatment), ***and***
- 50% or greater reduction in MBL volume from Baseline to the Final Month (last 28 days of treatment).

Secondary Efficacy Endpoints Included:

- Percentage of subjects with MBL volume < 80 mL and 50% or greater reduction in MBL volume from Baseline during the last 84 to 57 days and last 56 to 29 days of last treatment.
- Percentage of subjects with MBL volume < 80 mL at the Final Month (last 28 days of treatment).
- Percentage of subjects with 50% or greater reduction in MBL volume from Baseline to the Final Month (last 28 days of treatment).
- Percentage of subjects with amenorrhea.
- Percentage of subjects with suppression of bleeding (no bleeding excluding spotting).
- Change from Baseline in percent of days of menstrual bleeding as reported in subject daily bleeding diary.
- Change from Baseline in menstrual bleeding scores as reported in subject eDiary.
- Percentage change from Baseline during treatment in uterine volume and fibroid volume at Month 3, Month 6 and Final Visit.
- Change from Baseline to each visit based on nonbleeding symptom associated with uterine fibroids.
- Percentage of subjects with ≥ 25% reduction in total fibroid volume.
- Percentage of subjects with ≥ 25% reduction in primary fibroid volume.
- Percentage of subjects with ≥ 25% reduction in uterine volume.
- Percentage of subjects who successfully avoid surgical or invasive procedures for uterine fibroids.
- Change from Baseline to Final Visit during treatment in hemoglobin concentration.

Exploratory endpoints include:

- Change from Baseline in bone biomarker parameters
- Lipoprotein analysis by nuclear magnetic resonance, apolipoprotein B, and high sensitivity C-reactive protein

Criteria for Evaluation (Continued)

Efficacy (Continued):

Secondary Efficacy Endpoints Included (Continued):

Quality of life endpoints include:

- Non-Bleeding Uterine Fibroids Symptom Questionnaire (NBUFSQ)
- Change from Baseline in the Uterine Fibroid Symptom Quality of Life Questionnaire (UFS-QoL) score.
- Change from Baseline in the 12-Items Short Form Survey (SF-12).
- Change from Baseline in EuroQol-5D-5 level (EQ-5D-5L).
- Physicians' responses to the Surgery Intention Questionnaire (PSIQ).
- Subjects' responses to the Surgery Intention Questionnaire (SSIQ).
- Response at each month in the Patient Global Impression of Change (PGIC) questionnaires:
  - Menstrual Bleeding (PGIC-MB)
  - Non-Bleeding Uterine Fibroid Symptoms (PGIC-NBUFS)
- Response to the Post-Treatment Patient Global Impression of Change (PPGIC) questionnaires:
  - Menstrual Bleeding (PPGIC-MB)
  - Non-Bleeding Uterine Fibroid Symptoms (PPGIC-NBUFS)
- Change from Baseline to each visit in Health-Related Productivity Questionnaire (HRPQ) scores.
- Uterine fibroids related number of non-study health visits, number of days in hospital and type of procedures performed based on Health Resource Utilization Questionnaire (HRUQ).
- Response based on reasons for Study Participation Questionnaire.

Pharmacodynamic:

Concentrations of estradiol, progesterone, luteinizing hormone (LH), and FSH were obtained throughout the study duration.

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, endometrial thickness, ovarian cysts, return to Post-Treatment menses, and exploratory bone biomarkers.

Statistical Methods

Efficacy:

Primary Analysis of Primary Endpoint

The primary endpoint was analyzed using a logistic regression model including treatment as the main factor and baseline MBL volume as a covariate to compare each elagolix dosing group to placebo.

Analyses for Secondary Efficacy Endpoints

For continuous variables, including change and percentage change from Baseline analyses, treatment group differences were generally analyzed using analysis of covariance (ANCOVA) models with treatment group as the main effect and corresponding baseline value as a covariate.

Categorical data were analyzed using chi-square, Fisher's exact test, or logistics regression as appropriate.

Pharmacokinetic/Pharmacodynamic:

Plasma concentrations of elagolix and hormones were listed for each subject by visit day and dose regimen.

Safety:

Safety analyses included AEs, laboratory parameters, vital sign parameters, 12-lead electrocardiogram (ECG), and safety endpoints of BMD, bone biomarkers, post-treatment menses, endometrial safety via transvaginal ultrasound (TVU)/transabdominal ultrasound (TAU) and endometrial biopsy, and pregnancy results.

For continuous variables, descriptive statistics (mean, standard deviation, median, minimum, and maximum) were summarized by treatment group.

The treatment group differences in change and percentage change from baseline were generally analyzed using a 1-way analysis of variance (ANOVA) with treatment as the main effect.

Categorical data were summarized with frequencies and percentages by treatment group. Chi-square test or Fisher's exact test were used to analyze treatment group differences for qualitative categorical variables as appropriate.

Summary/Conclusions

Efficacy Results:

Primary Efficacy Endpoint

All elagolix treatment groups in both cohorts met the primary efficacy endpoint, with a statistically significantly greater proportion of responders (all, $P < 0.001$) compared with that of placebo.

In Cohort 1, the largest effect was seen with elagolix 300 mg BID alone; responder rates were 92% for elagolix 300 mg BID, 85% for elagolix 300 mg BID + LD E2/NETA, and 79% for elagolix 300 mg BID + SD E2/NETA compared with 27% for placebo.

For Cohort 2, results were comparable to Cohort 1. Responder rates in Cohort 2 were 90% for elagolix 600 mg QD, 73% for elagolix 600 mg QD + LD E2/NETA, and 82% for elagolix 600 mg QD + SD E2/NETA compared with 32% for placebo.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Secondary Endpoints Related to Reduction of HMB

Generally, there was a statistically significant effect of elagolix on most of the secondary efficacy endpoints related to reduction of HMB in both cohorts.

In Cohort 1, the percentages of subjects who achieved an MBL volume < 80 mL at the Final Month were statistically significantly higher (all, $P < 0.001$) relative to placebo (33% of subjects) with elagolix 300 mg BID, elagolix 300 mg BID + LD E2/NETA, and elagolix 300 mg BID + SD E2/NETA (92%, 89%, and 79% of subjects, respectively).

In Cohort 2, results were comparable to Cohort 1. The percentages of subjects with MBL volume < 80 mL at the Final Month were statistically significantly higher (all, $P < 0.001$) relative to placebo (37% of subjects) with elagolix 600 mg QD, elagolix 600 mg QD + LD E2/NETA, and elagolix 600 mg QD + SD E2/NETA (92%, 73%, and 86% of subjects, respectively).

In both cohorts, the analysis of mean percentage change from baseline to Final Month in MBL showed a percentage reduction in MBL that was statistically significant (all, $P < 0.001$) for all elagolix treatment groups (Cohort 1, –24% for placebo, –93% for elagolix 300 mg BID, –81% for elagolix 300 mg BID + LD E2/NETA, and –71% for elagolix 300 mg BID + SD E2/NETA; Cohort 2, –25% for placebo, –88% for elagolix 600 mg QD, –69% for elagolix 600 mg QD + LD E2/NETA, and –79% for elagolix 600 mg QD + SD E2/NETA).

The percentage of subjects with suppression of bleeding (no bleeding excluding spotting) and the percentage of subjects with amenorrhea were statistically significantly higher in all elagolix treatment groups relative to placebo in each cohort (all, $P < 0.001$).

In both cohorts, the mean changes from Baseline to Month 6 and Final Visit in hemoglobin concentration (g/dL) were statistically significantly higher in all elagolix treatment groups relative to placebo (all, $P \leq 0.001$).

A larger percentage of subjects in the elagolix treatment groups experienced a change from Baseline in hemoglobin concentration of ≥ 1.0 g/dL relative to placebo. At Month 6, 88% of subjects in the elagolix 300 mg BID alone group, 72% of subjects in the elagolix 300 mg BID + LD E2/NETA group, and 65% of subjects in the elagolix 300 mg BID + SD E2/NETA group had an increase in hemoglobin concentration of ≥ 1.0 g/dL compared with 32% in the placebo group. The percentages of subjects with a change from Baseline in hemoglobin concentration of ≥ 1.0 g/dL at Month 6 in the elagolix 600 mg QD (alone, + LD E2/NETA and + SD E2/NETA) groups were comparable within Cohort 2 (ranging from 58% to 63%).

Secondary Endpoints Related to Fibroid and Uterine Volumes

In both cohorts, the mean percentage reductions from Baseline to Month 6, and Final Visit in primary and total fibroid volume were statistically significantly greater in the elagolix alone (300 mg BID or 600 mg QD) and elagolix (300 mg BID or 600 mg QD) + LD E2/NETA groups relative to placebo.

In both cohorts, the mean percentage reductions from Baseline to Month 3, Month 6, and Final Visit in uterine volume were statistically significantly greater in all elagolix treatment groups relative to placebo.

The reductions in fibroid and uterine volume with elagolix treatment alone were generally attenuated in a dose-dependent fashion by add-back therapy with E2/NETA.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Patient-Reported Outcomes

UFS-QoL:

In both cohorts, the mean reductions from Baseline to Month 6 in the symptom severity score was statistically significantly greater and the mean change in the Health Related Quality of Life Questionnaire (HRQL) total score was statistically significantly higher in each elagolix treatment group relative to placebo (higher symptom severity scores and lower HRQL total scores indicate worse symptoms and lesser QoL).

EQ-5D-5L:

In Cohort 1, the mean change from Baseline to Month 6 in the EQ-5D-5L index was statistically significantly higher in all elagolix treatment groups relative to placebo. No statistically significant differences in the mean change from Baseline to Month 6 were observed between the elagolix treatment groups and placebo in Cohort 2. An increase in this index indicates a positive impact on health state.

PGIC-MB and PGIC-NBUFS:

The percentages of subjects who responded to PGIC-MB or PGIC-NBUFS with "very much improved" or "much improved" in all elagolix treatment groups at Month 6 were statistically significantly larger than that of placebo in both cohorts for PGIC-MB and in Cohort 2 for PGIC-NBUFS.

Efficacy Summary

The study's primary efficacy endpoint was met at Final Month in all elagolix treatment groups (300 mg BID or 600 mg QD alone and with LD or SD E2/NETA). In addition, numerical and/or statistically significant improvements were seen for both elagolix regimens (300 mg BID and 600 mg QD) compared with placebo for almost all of the key secondary endpoints that were evaluated. These findings suggest that elagolix has the potential to provide significant benefits in the management of HMB in premenopausal women.

Pharmacokinetic Results:

For both cohorts, the greatest suppression of estradiol, progesterone, and LH was observed in the elagolix alone groups, compared with that of placebo. Coadministration of E2/NETA with elagolix partially attenuated the suppression of estradiol and LH in a dose-dependent fashion compared to when elagolix was dosed alone. FSH was further suppressed with the coadministration of E2/NETA.

Safety Results:

Hot flush, headache, and nausea were the most common AEs in the elagolix treatment groups, consistent with previous elagolix studies. The majority of treatment-emergent AEs were mild or moderate in severity, and the most frequently reported severe AE in the elagolix treatment groups was hot flush. Nausea and hot flush were the most common AEs leading to study drug discontinuation in the elagolix treatment groups, and menorrhagia was the most frequently reported AE leading to discontinuation in the placebo groups.

Summary/Conclusions (Continued)

Safety Results (Continued):

Adverse Events

Treatment-emergent AEs were reported by the majority of subjects, and the proportion of subjects who experienced an AE was highest in the elagolix alone groups.

In Cohort 1, 47 subjects (72.3%) in the placebo group, 52 (80.0%) in the elagolix 300 mg BID alone group, 47 (73.4%) in the elagolix 300 mg BID + LD E2/NETA group, and 48 (73.8%) in the elagolix 300 mg BID + SD E2/NETA group reported at least 1 treatment-emergent AE.

In Cohort 2, 53 subjects (67.9%) in the placebo group, 67 (87.0%) in the elagolix 600 mg QD alone group, 56 (73.7%) in the elagolix 600 mg QD + LD E2/NETA group, and 55 subjects (71.4%) in the elagolix 600 mg QD + SD E2/NETA group reported at least 1 treatment-emergent AE. Overall, rates were similar across treatment groups for most AEs with the exception of bone density decreased and insomnia in Cohort 1; nausea, blood cholesterol increased, urinary tract infection, and back pain in Cohort 2; and headache, and hot flush in both cohorts. All of these AEs were reported more frequently in the elagolix treatment groups.

AEs resulting in study drug discontinuation were reported for 19 subjects in Cohort 1, including 7 subjects (10.8%) in the placebo group, 4 (6.2%) in the elagolix 300 mg BID alone group, 2 (3.1%) in the elagolix 300 mg BID + LD E2/NETA group, and 6 (9.2%) in the elagolix 300 mg BID + SD E2/NETA group. In Cohort 1, nausea and hot flush were the most common AEs leading to study drug discontinuation in the elagolix treatment groups, each reported by 3 subjects (1.5%) across all elagolix treatment groups. Menorrhagia was the most frequently reported AE leading to discontinuation in the placebo group, reported by 2 subjects (3.1%). AEs resulting in study drug discontinuation were reported for 28 subjects in Cohort 2, including 1 subject (1.3%) in the placebo group, 11 (14.3%) in the elagolix 600 mg QD alone group, 7 (9.2%) in the elagolix 600 mg QD + LD E2/NETA group, and 9 (11.7%) in the elagolix 600 mg QD + SD E2/NETA group. In Cohort 2, nausea and hot flush were the most common AEs leading to study drug discontinuation in the elagolix treatment groups, reported by 4 subjects (1.7%) and 3 subjects (1.3%), respectively, across all elagolix treatment groups. Anaemia was the only AE that led to discontinuation in the placebo group, reported by 1 subject (1.3%).

Treatment-emergent serious adverse events (SAEs) were reported for 13 subjects in Cohort 1, including 6 subjects (9.2%) in the placebo group, 3 (4.6%) in the elagolix 300 mg BID group, 3 (4.7%) in the elagolix 300 mg BID + LD E2/NETA group, and 1 (1.5%) in the elagolix 300 mg BID + SD E2/NETA group. Treatment-emergent SAEs were reported for 13 subjects in Cohort 2, including 1 subject (1.3%) in the placebo group, 5 (6.5%) in the elagolix 600 mg QD group, 3 (3.9%) in the elagolix 600 mg QD + LD E2/NETA group, and 4 (5.2%) in the elagolix 600 mg QD + SD E2/NETA group. In both cohorts, the majority of SAEs were reported by 1 subject each in any treatment group.

One subject in the elagolix 600 mg QD + LD E2/NETA group had an SAE of uterine leiomyoma that was considered reasonably possibly related to study drug.

SAEs with onset from study end Day 31 through study end Day 60 during the Post-Treatment Follow-Up Period were reported for 6 subjects overall.

Summary/Conclusions (Continued)

Safety Results (Continued):

Serum Lipids

In Cohort 1, the elagolix 300 mg BID group showed statistically significant or numerical increases in mean percentage changes from Baseline in total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides compared to placebo at Month 6 (all, $P \leq 0.05$). The increases in LDL-C/HDL-C ratios and total cholesterol/HDL-C ratios were minimal due to concomitant increases in HDL-C. The lipid changes observed in the elagolix 300 mg BID group were attenuated with E2/NETA in a dose-dependent fashion. Similar results were seen in Cohort 2. In general, with the exception of triglycerides, increases in serum lipids occurred within 1 to 2 months after the start of elagolix treatment and remained elevated thereafter for elagolix treatment groups in both cohorts. Serum lipid parameters, which had increased during the Treatment Period, returned to baseline levels by Post-Treatment Follow-Up Month 3.

BMD Changes During the Treatment Period

In Cohort 1, treatment with elagolix for 6 months was associated with mean percentage decreases in BMD at lumbar spine, total hip, and femoral neck, with the largest effect in the lumbar spine; these changes were attenuated by add-back therapy with E2/NETA, most effectively by SD E2/NETA. The mean percentage decreases in BMD were statistically significantly different relative to placebo in the elagolix 300 mg BID alone and elagolix 300 mg BID + LD E2/NETA groups at all anatomic locations; however, the difference with elagolix 300 mg BID + SD E2/NETA was not statistically significant at lumbar spine or femoral neck. Similar results were seen in Cohort 2.

Cohort 1: In lumbar spine BMD, the placebo group had a mean percentage increase from Baseline to Month 6 (0.913%), and the elagolix 300 mg BID alone and elagolix 300 mg BID + LD E2/NETA groups had mean percentage decreases from Baseline to Month 6 (–3.797%, –1.623%, respectively) that were statistically significantly different relative to placebo (–4.709%, 95% CI: –5.8305, –3.5880, $P < 0.001$; –2.536%, 95% CI: –3.6569, –1.4144, $P < 0.001$, respectively); however, the decrease with elagolix 300 mg BID + SD E2/NETA (–0.141%) was not statistically significant (–1.053%, 95% CI: –2.1746, 0.0680, $P = 0.065$). Similar results were seen in total hip and femoral neck.

Cohort 2: In lumbar spine BMD, the placebo group had a mean percentage decrease from Baseline to Month 6 (–0.125%), and the elagolix 600 mg QD alone and elagolix 600 mg QD + LD E2/NETA groups had mean percentage decreases from Baseline to Month 6 (–3.403%, –1.235%, respectively) that were statistically significantly different from that of placebo (–3.279%, 95% CI: –4.2721, –2.2850, $P < 0.001$; –1.111%, 95% CI: –2.1623, –0.0587, $P = 0.039$, respectively); however, the decrease with elagolix 600 mg QD + SD E2/NETA (–1.111%) was not statistically significant (–0.986%, 95% CI: –2.0032, 0.0315, $P = 0.057$). Similar results were seen in total hip and femoral neck.

BMD Changes During the Post-Treatment Follow-Up Period

For subjects who had DXA measurements in the Post-Treatment Follow-Up Period, mean percentage decreases in BMD at Post-Treatment Follow-Up Month 6 were comparable to placebo in all elagolix treatment groups, with exception of elagolix 300 mg BID alone in total hip and elagolix 600 mg QD alone at lumbar spine, which were statistically different relative to placebo.

Summary/Conclusions (Continued)

Safety Results (Continued):

Categorical Summary of BMD Changes

Generally, the majority of subjects in the placebo groups were distributed among the categories of no change or increase, > 0% to ≤ 1.5% decrease, and > 1.5% to ≤ 3% decrease in BMD in all anatomic locations of both cohorts. Treatment with elagolix 300 mg BID or elagolix 600 mg QD shifted the distribution of subjects so that the majority was in categories of greater decrease: > 1.5% to ≤ 3% decrease, > 3% to ≤ 5% decrease, > 5% to < 8% decrease, and ≥ 8% decrease. In lumbar spine in Cohort 1, 4.6% of subjects in the placebo group were distributed in the BMD categories of > 3% to ≤ 5% decrease and > 5% to < 8% decrease, and the percentage of subjects in these categories increased to 48% in the elagolix 300 mg BID group. This change in distribution was partially attenuated in a dose-dependent fashion by add-back therapy with E2/NETA, with 22.9% of subjects and 10.5% of subjects in the BMD categories of > 3% to ≤ 5% decrease and > 5% to < 8% decrease in the elagolix 300 mg BID +LD E2/NETA and elagolix 300 mg BID + SD E2/NETA groups, respectively, which was statistically significantly different from the distribution of subjects in the elagolix 300 mg BID group. Similar changes in distribution were seen at all anatomic locations and in both cohorts.

Categorical Summary of BMD Changes During the Post-Treatment Follow-Up Period

For subjects who had to have DXA measurements in the Post-Treatment Follow-Up Period, generally, by Post-Treatment Follow-Up Month 6, the distribution of larger proportions of subjects into BMD change categories of greater BMD loss that occurred with elagolix treatment during the Treatment Period had returned to a pattern that was similar to placebo, with the exception of elagolix 300 mg BID + SD E2/NETA at femoral neck (statistically significantly different compared to placebo).

Endometrial Safety

No abnormal biopsy findings were seen during the Treatment Period. In the placebo group of both cohorts, mean endometrial thickness increased slightly from Baseline to Month 6. In Cohort 1, all elagolix treatment groups showed a decrease in mean endometrial thickness from Baseline to Month 6, and this was statistically significantly different from the mean increase with placebo for elagolix 300 mg BID + LD E2/NETA. In Cohort 2, all elagolix treatment groups showed a decrease in mean endometrial thickness from Baseline to Month 6, and this was statistically significantly different from the mean increase with placebo with elagolix 600 mg QD alone.

Pregnancies

One pregnancy was reported during the study; this occurred in the elagolix 600 mg QD alone group. The outcome was elective abortion, and the pregnancy led to study drug discontinuation.

Summary/Conclusions (Continued)

Conclusions:

The study met its primary efficacy endpoint, with each elagolix treatment group showing a statistically significantly greater proportion of responders who achieved MBL volume of < 80 mL at the Final Month and 50% or greater reduction in MBL volume from Baseline to the Final Month compared with that of the placebo group. The results from this Phase 2b dose-finding study confirmed that elagolix (600 mg total daily dose) provides significant benefits in the management of HMB associated with uterine fibroids in premenopausal women. The overall incidence of AEs was highest in the elagolix alone (300 mg BID or 600 mg QD) group in each cohort, and this was attenuated by add-back therapy with E2/NETA. The majority of treatment-emergent AEs were mild or moderate in severity, and the most frequently reported severe AE in the elagolix treatment groups was hot flush. Generally, no potentially clinically meaningful changes in most laboratory parameters and vital signs were seen, except for statistically significant reductions in BMD and increases in serum lipids (minimal increases in key serum lipid ratios), all of which were attenuated in a dose dependent fashion when elagolix was taken with E2/NETA.

The elagolix 300 mg BID regimen had better tolerability than the elagolix 600 mg QD regimen. Hormonal add-back therapy with SD E2/NETA more effectively attenuated the side effects on BMD, serum lipids, and hypoestrogenic AEs compared to LD E2/NETA and was associated with a high level of efficacy. Therefore, elagolix 300 mg BID + SD E2/NETA was chosen as the dose to be evaluated in the Phase 3 development program.