Long-Term Outcomes of Elagolix in Women With Endometriosis

Results From Two Extension Studies

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OBJECTIVE: To evaluate the efficacy and safety of elagolix, an oral, nonpeptide gonadotropin-releasing hormone antagonist, over 12 months in women with endometriosis-associated pain.

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METHODS: Elaris Endometriosis (EM)-III and -IV were extension studies that evaluated an additional 6 months of treatment after two 6-month, double-blind, placebo-controlled phase 3 trials (12 continuous treatment months) with two elagolix doses (150 mg once daily and 200 mg twice daily). Coprimary efficacy endpoints were the proportion of responders (clinically meaningful pain reduction and stable or decreased rescue analgesic use) based on average monthly dysmenorrhea and nonmenstrual pelvic pain scores. Safety assessments included adverse events, clinical laboratory tests, and endometrial and bone mineral density assessments. The power of Elaris EM-III and -IV was based on the comparison to placebo in Elaris EM-I and -II with an expected 25% dropout rate.

RESULTS: Between December 28, 2012, and October 31, 2014 (Elaris EM-III), and between May 27, 2014, and January 6, 2016 (Elaris EM-IV), 569 participants were enrolled. After 12 months of treatment, Elaris EM-III responder rates for dysmenorrhea were 52.1% at 150 mg once daily (Elaris EM-IV=50.8%) and 78.1% at 200 mg twice daily (Elaris EM-IV=75.9%). Elaris EM-III nonmenstrual pelvic pain responder rates were 67.8% at 150 mg once daily (Elaris EM-IV=66.4%) and 69.1% at 200 mg twice daily (Elaris EM-IV=67.2%). After 12 months of treatment, Elaris EM-III dyspareunia responder rates were 45.2% at 150 mg once daily (Elaris EM-IV=45.9%) and 60.0% at 200 mg twice daily (Elaris EM-IV=58.1%). Hot flush was the most common adverse event. Decreases from baseline in bone mineral density and increases from baseline in lipids were observed after 12 months of treatment. There were no adverse endometrial findings.

CONCLUSION: Long-term elagolix treatment provided sustained reductions in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia. The safety was consistent with reduced estrogen levels and no new safety concerns were associated with long-term elagolix use.

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Endometriosis is a chronic disease with debilitating pain symptoms that affects 6–10% of women of reproductive age.[1–7] There is an unmet need for an oral, long-term treatment that adequately manages endometriosis symptoms while minimizing negative side effects.[1,3,8,9] First-line medical therapies for endometriosis-related pain (eg, combined oral contraceptives, progestins) have limited long-term efficacy and second-line therapies (eg, high-dose progestins, injectable depot formulations of gonadotropin-releasing hormone [GnRH] agonists) are effective but associated with troublesome side effects including progressive bone loss and severe vasomotor symptoms.[3,10–17]

Elagolix is an oral, nonpeptide GnRH antagonist. Phase 1 and 2 studies showed that elagolix suppressed estradiol production in a dose-dependent manner with partial suppression at a once-daily 150-mg dose and nearly full suppression with 200 mg twice daily[18] while demonstrating efficacy and an acceptable safety profile in women with endometriosis.[18–20] Two double-blind, placebo-controlled phase 3 trials (Elaris Endometriosis EM-I and Elaris EM-II) demonstrated that 6 months of elagolix treatment with both 150 mg once daily and 200-mg twice-daily doses resulted in an acceptable safety profile and clinically significant reductions in dysmenorrhea and nonmenstrual pelvic pain in women with moderate to severe endometriosis-associated pain compared with placebo.[21]

We report the results of two similar 6-month, double-blind, phase 3 extension studies (Elaris EM-III and Elaris EM-IV) of the preceding 6-month, double-blind, placebo-controlled trials.[21] These extension studies evaluated long-term efficacy and safety of elagolix for the management of endometriosis-associated pain in women who received elagolix for 12 continuous months.

MATERIALS AND METHODS

Elaris EM-III and Elaris EM-IV were two 6-month, phase 3, randomized, double-blind, extension studies that enrolled women who completed one of the two preceding 6-month, phase 3, randomized, double-blind, placebo-controlled trials (Elaris EM-I and Elaris EM-II, described previously[21]) (Appendix 1, available online at http://links.lww.com/AOG/B100). Data from women who received placebo in Elaris EM-I and Elaris EM-II and then were switched to elagolix for up to 6 months in Elaris EM-III and Elaris EM-IV will be reported in a separate publication because these data do not reflect the long-term treatment effects of elagolix.

Participants were enrolled at 151 sites across the United States, Puerto Rico, and Canada between December 28, 2012, and October 31, 2014, and at 148 sites across five continents between May 27, 2014, and January 6, 2016. Participants were premenopausal women, between 18 and 49 years old, who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain at the time of entry in the preceding Elaris EM-I and Elaris EM-II trials.[21] Eligible consenting women entered the extension study after completing the 6-month treatment period in the preceding Elaris EM-I and Elaris EM-II trials. Women were excluded if after the first 6 months of treatment they

had a bone mineral density (BMD) decrease from baseline 8% or greater in the spine, femoral neck, or total hip or if they had a clinically significant condition detected in Elaris EM-I or Elaris EM-II (Fig. 1).

The extension studies (Elaris EM-III and Elaris EM-IV) consisted of two periods: a 6-month treatment period and a posttreatment follow-up period of up to 12 months. Women on elagolix treatment in the preceding Elaris EM-I and Elaris EM-II trials who met all entry criteria received the same elagolix dose as previously taken, either elagolix 150 mg daily or elagolix 200 mg twice daily, for 6 additional months in the extension studies. Study participants, investigators, and site personnel remained blinded to the participant's original treatment from the preceding Elaris EM-I and Elaris EM-II trials throughout these extension studies. The elagolix 150-mg dose or its identical placebo was administered as a single pill in the morning. The elagolix 200-mg dose or its identical placebo was administered as two pills twice a day in the morning and the evening. Overall, each woman took three pills in the morning and two pills in the evening to maintain the blinding between dose groups. Any other hormonal therapy (eg, hormonal forms of birth control) was discontinued during the

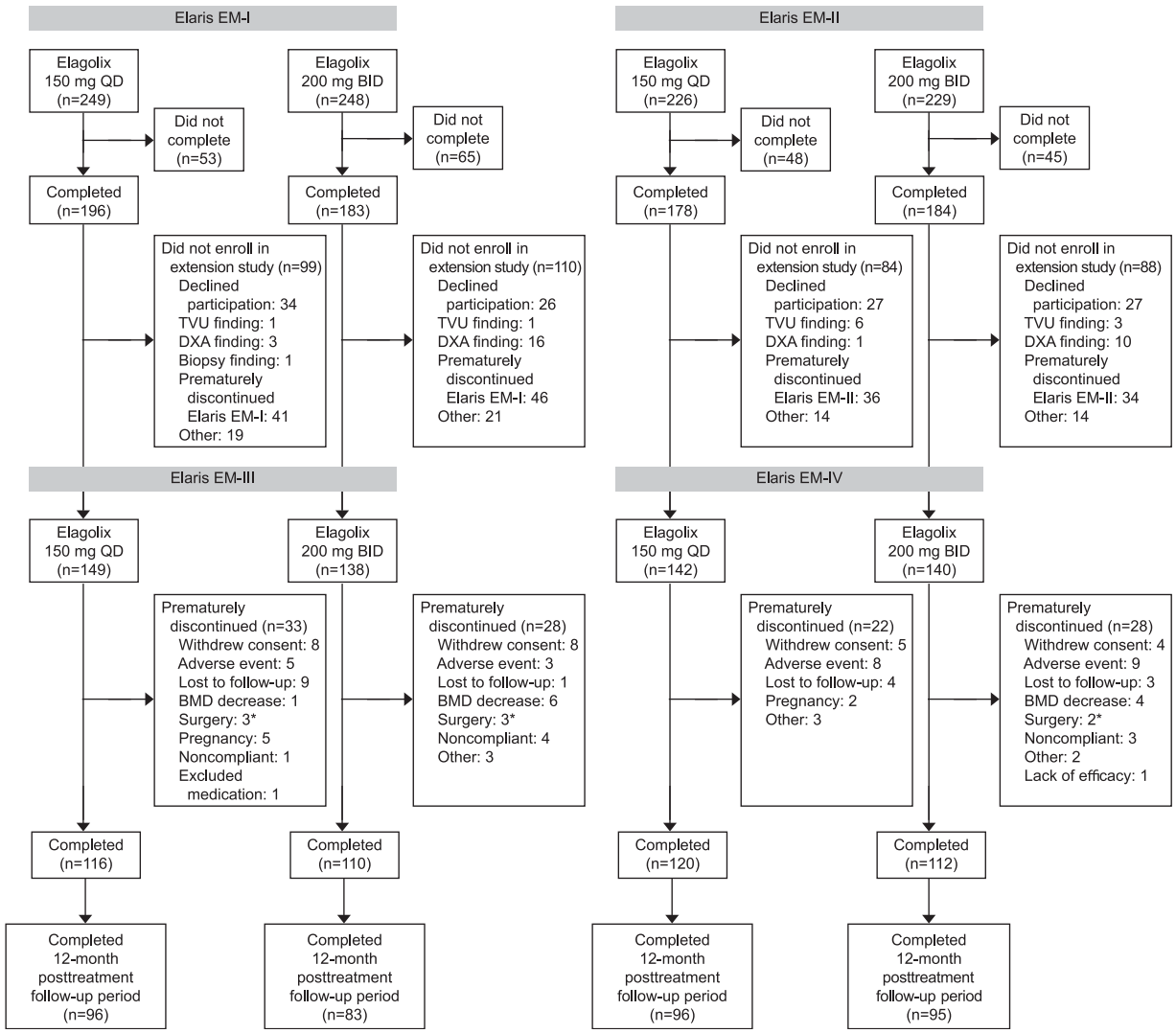

Fig. 1. Patient disposition. *Women required surgery or invasive intervention for endometriosis. QD, once daily; BID, twice daily; BMD, bone mineral density; TVU, transvaginal ultrasonography; DXA, dual-energy X-ray absorptiometry; EM, endometriosis.

Surrey. Long-Term Efficacy and Safety of Elagolix. Obstet Gynecol 2018.

washout period in the preceding Elaris EM-I and Elaris EM-II trials and women were instructed to remain off hormone therapies and to use two forms of nonhormonal contraceptives during the extension studies, as previously required for the preceding double-blind, placebo-controlled trials (see Appendix 1, http://links.lww.com/AOG/B100, for timing of washout and screening periods). Monthly pregnancy tests were performed during the extension treatment period and the first 6 months of follow-up. Women were instructed to take 400 international units vitamin D with 500–1,000 mg calcium throughout the study (vitamin D and calcium supplements were provided based on availability and in accordance with local regulations). If needed, women continued to receive the allowed rescue medication of a nonsteroidal antiinflammatory drugs (500 mg naproxen), an opioid according to country (eg, 5 mg hydrocodone plus 325 mg acetaminophen), or both during the extension studies. Treatment period study visits were performed on day 1 (the day of the first study drug dose in the extension study) and monthly through 6 months. Posttreatment follow-up study visits were required for all women, posttreatment follow-up month 1 through posttreatment follow-up month 6 (posttreatment follow-up dual-energy X-ray absorptiometry [DXA] was not required for all women; see safety methods); posttreatment follow-up study visits during months 7–12 were based on BMD and menstrual cycle assessment results. Some women received elagolix for greater than 6 months in the preceding double-blind, placebo-controlled trials while individual eligibility for extension study enrollment was assessed.

Elaris EM-III and Elaris EM-IV were conducted in accordance with International Conference on Harmonization guidelines and applicable regulations and ethical principles of the Declaration of Helsinki. The study protocols were approved by the institutional review board or ethics committee for each study site in all participating countries. All women provided written informed consent for entry into these extension studies. The data reported in the current publication were funded by AbbVie, Inc and for each study AbbVie participated in the study design, research, data collection, data analysis, interpretation of the data, and writing, reviewing, and approving the publication. All recommendations specified by the Good Publication Practice guidelines for industry-sponsored research were adhered to.

Women used an electronic diary (e-diary) to report daily pain assessments, rescue analgesic use, and uterine bleeding. The efficacy endpoints of primary interest were the proportion of responders for dysmenorrhea and nonmenstrual pelvic pain (each measured by the e-diary on a 4-point pain effect scale ranging from 0 [no pain] to 3 [severe pain]), taking into account the use of rescue analgesic medication for endometriosis-associated pain after 12 months of treatment, consistent with the coprimary endpoints in the preceding double blind, placebo-controlled trials. For each of these endpoints, the criteria for defining a woman as a responder required both a clinically meaningful reduction in pain based on a response threshold derived using a receiver operating characteristics analysis from the preceding double-blind, placebo-controlled trials (Elaris EM-I and Elaris EM-II)[21] and reduced or stable rescue analgesic use. The receiver operating characteristics analysis defined the threshold for a clinically meaningful change from baseline for both dysmenorrhea and nonmenstrual pelvic pain separately in each trial, based on the use of patient reports of much improved and very much improved on the patient global impression of change as an anchor. The pain scores and rescue analgesic use were averaged over the 35-day window before and including the study visit day.

Secondary efficacy variables included the proportion of dyspareunia responders after 12 months of treatment, mean changes from baseline to each treatment month for dysmenorrhea, nonmenstrual pelvic pain, dyspareunia, overall endometriosis-associated pain scores (numeric rating scale score), and use of rescue analgesic agents at baseline and after 12 months of treatment (both nonsteroidal antiinflammatory drugs and opioid pills). Secondary efficacy variables also included the results of the Patient Global Impression of Change and 30-item Endometriosis Health Profile questionnaires at baseline and after 12 months of treatment.

Treatment-emergent adverse events (events that occurred after treatment began) were monitored. Adverse events were coded with the use of the Medical Dictionary for Regulatory Activities 18.1 (Elaris EM-III) and 19.1 (Elaris EM-IV) and categorized by the study investigator as mild, moderate, or severe and as having a reasonable possibility or no reasonable possibility of being related to treatment. Serious adverse events were also recorded; serious adverse events were those events considered by the investigator to be life-threatening, require hospitalization or medical or surgical intervention to prevent serious events, or those that resulted in death or persistent disability or incapacity.

Bone mineral density of the lumbar spine, total hip, and femoral neck was measured after 12 months of treatment and, if required by protocol, 6 and 12 months posttreatment by DXA. In Elaris EM-III, women were only required to have a follow-up DXA at 6 and 12 months posttreatment if they had a decrease greater than 1.5% from baseline in the lumbar spine or a decrease greater than 2.5% in total hip at their prior DXA scan or at premature discontinuation. Elaris EM-III was not designed to collect and evaluate posttreatment BMD recovery, is not a reliable indicator for BMD changes off therapy, and therefore posttreatment follow-up BMD data from this study are not presented. For Elaris EM-IV, all women were required to have a follow-up DXA at 6 months posttreatment and women were required to have a follow-up DXA at 12 months posttreatment if they had a decrease greater than 1.5% from baseline in the lumbar spine or a decrease greater than 2.5% in total hip BMD at 6 months posttreatment. Dual-energy X-ray absorptiometry results were evaluated by a blinded central reader to ensure that inappropriate lumbar spine sites were not included.

Endometrial biopsies were conducted in Elaris EM-III only and evaluated by two blinded central readers; the blinded readers' consensus was reported per the protocol. Transvaginal ultrasonograms were conducted within 10 days of menstruation during screening and after 12 months of treatment or at the time of premature discontinuation in the extension studies, regardless of the menstrual cycle stage. Transvaginal ultrasonograms were evaluated by a blinded central reader. Endometrial biopsy and transvaginal ultrasound results are reported at baseline and after 12 months of treatment.

Women recorded their uterine bleeding in the daily e-diary that asked whether they had any uterine bleeding in the previous 24 hours; the answers were recoded as spotting, light, medium, or heavy if the woman answered "yes" and none if the woman answered "no." Days with missing electronic diary entries were considered "no bleeding" days. Amenorrhea was assessed based on a 28-day window. Clinical laboratory tests, including plasma lipids, were performed at baseline, monthly during treatment, and at month 1 and month 3 posttreatment; change from baseline for plasma lipid data is reported at baseline, after 12 months of treatment, and at posttreatment month 1.

The extension studies were powered based on the previously reported Elaris EM-I and Elaris EM-II trials.[21] SAS was used to perform the statistical analyses. Baseline efficacy and safety analyses were performed in the modified intention-to-treat population, which included all women who received at least one dose of elagolix in the extension studies. Baseline was before dosing in the preceding double-blind, placebo-controlled trials.[21] Month 6 efficacy and safety data from the preceding double-blind, placebo-controlled trials include only the women who enrolled in the extension studies.

For efficacy outcomes, the mean change from baseline analyses were summarized with descriptive statistics; women with assessments at both baseline and the given time points were included in the analysis. Categorical assessments were summarized with frequencies and percentages. Statistical comparisons between dose groups were not prespecified and not performed because the extension studies were not designed or powered for these analyses.

Change from baseline in BMD and endometrial thickness, endometrial biopsy results, plasma lipid values, and adverse events were summarized for each treatment group with descriptive statistics. The number and percentage of women with BMD changes in specified categories (change 8% or greater decrease, greater than 5% to less than 8% decrease, greater than 3% to 5% or less decrease, 3% or less decrease) were also summarized. Bone mass density Z-scores were plotted across the treatment (Elaris EM-III and -IV) and posttreatment periods (Elaris EM-IV only). The proportion of women with amenorrhea during each treatment month and the proportion of women who reported a menses during posttreatment month 1 were summarized.

RESULTS

In total, 569 women were enrolled across both extension studies. Of the 287 women enrolled in the Elaris EM-III extension study, 226 (78.7%) completed the 6-month treatment period (150 mg once daily=77.9%; 200 mg twice daily=79.7%). For the Elaris EM-IV extension study, 232 of 282 (82.3%) enrolled women completed the 6-month treatment period (150 mg once daily=84.5%; 200 mg twice daily=80.0%) (Fig. 1). Reasons for study discontinuation are presented in Figure 1. Baseline demographics and clinical characteristics were representative of the study population characteristics of the preceding double-blind, placebo-controlled trials[21] and are presented in Table 1. The mean (SD, minimum–maximum) days of treatment exposure across Elaris EM-I and -III were 331.2 (45.2, 177–414) days at 150 mg once daily and 333.4 (46.4, 173–421) days at 200 mg twice daily; across Elaris EM-II and -IV mean (SD, minimum–maximum) days of treatment exposure were 342.0

(41.7, 177–420) days at 150 mg once daily and 335.3 (42.2, 187–408) days at 200 mg twice daily.

In Elaris EM-III, the percentage of women who had a clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents after 12 months was 52.1% in the 150-mg once-daily dose group and 78.1% in the 200-mg twice-daily group; in Elaris EM-IV, the corresponding percentages were 50.8% and 75.9% (Table 2). In Elaris EM-III, the percentage of women who had a clinically meaningful reduction in nonmenstrual pelvic pain and decreased or stable use of rescue analgesic agents after 12 months of treatment was 67.5% in the 150-mg once-daily dose group and 69.1% in the 200-mg twice-daily group; in Elaris EM-IV, the corresponding percentages were 66.4% and 67.2% (Table 2). Similar results were observed for dyspareunia in both extension studies. In Elaris EM-III, the percentage of women who had a clinically meaningful reduction in dyspareunia and decreased or stable use of rescue analgesic agents after 12 months of treatment was 45.2% in the 150-mg once-daily dose group and 60.0% in the 200-mg twice-daily dose group; in Elaris EM-IV, the corresponding percentages were 45.9% and 58.1% (Table 2). Decreased dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia scores from baseline were sustained through 12 months of treatment in each dose group (Fig. 2).

Mean decreases from baseline in average daily rescue analgesic pill count were observed at every visit during the extension study treatment period for nonsteroidal antiinflammatory drugs or opioid use in each dose group in Elaris EM-III and Elaris EM-IV (Appendix 2, available online at http://links.lww.com/AOG/B100).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline*

	Elaris EM-III		Elaris EM-IV	
Characteristic	Elagolix 150 mg QD (n=149)	Elagolix 200 mg BID (n=138)	Elagolix 150 mg QD (n=142)	Elagolix 200 mg BID (n=140)
Age (y)	32 (19–48)	31 (18–47)	33 (20–48)	34 (18–47)
Race				
White	89.3	91.3	89.4	90.0
Black	8.1	6.5	9.9	8.6
Other	2.7	2.2	0.7	1.4
BMI (kg/m^2)	28.8±6.4	28.3±6.5	26.5±6.3	26.9±6.5
Time since surgical diagnosis (mo)	45.5±28.2	49.4±26.3	45.6±34.7	56.6±42.6
Dysmenorrhea (score)†	2.1±0.4	2.2±0.5	2.1±0.5	2.1±0.5
Nonmenstrual pelvic pain (score)†	1.6±0.5	1.5±0.5	1.6±0.5	1.6±0.6
Dyspareunia (score)†	1.4±0.8	1.6±0.8	1.5±0.9	1.4±0.8
Overall endometriosis-associated pain (score)‡	5.7±1.7	5.3±1.6	5.5±1.8	5.4±1.8
Mean LDL-C (mg/dL)	97.1	94.7	99.2	99.9
Mean HDL-C (mg/dL)	55.4	56.6	60.6	58.5
Mean triglycerides (mg/dL)	106	99.8	104	106
BMD (mean Z-score)				
Lumbar spine,	0.6	0.6	0.3	0.3
Total hip	0.6	0.4	0.3	0.3
Femoral neck	0.4	0.3	0.3	0.3
Analgesic use (% of women)				
NSAID only	23.5	34.1	34.5	30.7
Opioid only	18.1	18.8	17.6	10.7
NSAID and opioid	42.3	40.6	40.8	49.3
None	16.1	6.5	7.0	9.3

QD, once daily; BID, twice daily; BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BMD, bone mineral density; NSAID, nonsteroidal antiinflammatory drug.

Data are median (minimum–maximum), %, or mean±SD unless otherwise specified.

Because of rounding, percentages do not sum to 100%.

* Baseline was before dosing in the preceding double-blind, placebo-controlled trials (Elaris EM-I and -II).

† Pain scores range from 0 (none) to 3 (severe) and were recorded in a daily electronic diary. Scores for dyspareunia were analyzed for women who recorded data other than "not applicable" at baseline.

‡ Measured with the numeric rating scale; women provided daily self-assessments of overall endometriosis-associated pain on a scale of 0 (no pain) to 10 (worst pain ever).

Table 2. Proportion of Dysmenorrhea, Nonmenstrual Pelvic Pain, and Dyspareunia Responders After 6 and 12 Months of Elagolix Treatment

	Elaris EM-III		Elaris EM-IV	
Responders*	Elagolix 150 mg QD	Elagolix 200 mg BID	Elagolix 150 mg QD	Elagolix 200 mg BID
Dysmenorrhea				
6 mo of treatment†	60/149 (40.3)	109/136 (80.1)	72/142 (50.7)	107/140 (76.4)
12 mo of treatment‡	61/117 (52.1)	86/110 (78.2)	62/122 (50.8)	88/116 (75.9)
Nonmenstrual pelvic pain				
6 mo of treatment†	74/149 (49.7)	96/136 (70.6)	82/142 (57.7)	89/140 (63.6)
12 mo of treatment‡	79/117 (67.5)	76/110 (69.1)	81/122 (66.4)	78/116 (67.2)
Dyspareunia				
6 mo of treatment†	42/113 (37.2)	54/92 (58.7)	47/108 (43.5)	62/100 (62.0)
12 mo of treatment‡	38/84 (45.2)	42/70 (60.0)	39/85 (45.9)	43/74 (58.1)

QD, once daily; BID, twice daily.
Data are n/N (%).
Between-group comparisons were not predefined and not performed. Data are observed, nonmissing data.
* Responders had a clinically meaningful reduction in the respective type of pain and stable or decreased rescue analgesic use.
† Month 6 in the preceding double-blind, placebo-controlled trials; data are from women who enrolled in the extension studies.
‡ After an additional 6 months of treatment in the extension study; some women received greater than 6 months of additional elagolix treatment while individual eligibility for extension study enrollment was assessed (see Materials and Methods).

After 12 months of treatment, the use of opioids, based on average pill count, declined from baseline by 45.1% among women treated with elagolix 150 mg once daily (Elaris EM-IV=31.4%) and 74.6% among women treated with elagolix 200 mg twice daily (Elaris EM-IV=65.7%).

Reductions from baseline in overall endometriosis-associated pain, as measured by the numeric rating scale, were observed across dose groups and studies after 12 months of elagolix treatment (Appendix 2, http://links.lww.com/AOG/B100). A majority of women reported much or very much improved endometriosis-associated pain on the Patient Global Impression of Change after 12 months of treatment (Appendix 2, http://links.lww.com/AOG/B100). Twelve months of elagolix treatment was also associated with improved quality of life in all domains across dose groups and studies as evidenced by reduced Endometriosis Health Profile-30 dimension scores from baseline (lower Endometriosis Health Profile-30 scores reflect better quality of life) (Appendix 3, available online at http://links.lww.com/AOG/B100).

Approximately 90% of women treated with elagolix over the course of 12 months had at least one adverse event, which is comparable with the number of elagolix-treated women who experienced any adverse event during the preceding 6-month, double-blind, placebo-controlled studies (approximately 80–85% across studies and doses).[21] Less than 5% of women in either dose group in Elaris EM-III and less than 8% in either dose group in Elaris EM-IV had a serious adverse event (Table 3). The three most common adverse events during the 12 months of treatment were hot flush, headache, and nausea (Table 3; Appendix 4, available online at http://links.lww.com/AOG/B100). The maximum severity of hot flushes was mild or moderate in the majority of women in each dose group (Elaris EM-III 150 mg once daily: mild hot flush n/N=30/44, moderate hot flush n/N=12/44; Elaris EM-III 200 mg twice daily: mild hot flush n/N=40/72, moderate hot flush n/N=24/72; Elaris EM-IV 150 mg: once daily mild hot flush n/N=23/36, moderate hot flush n/N=13/36; Elaris EM-IV 200 mg twice daily: mild hot flush n/N=36/77, moderate hot flush n/N=38/77). The most common severe adverse event across dose groups was hot flush in Elaris EM-III (150 mg once daily n [%] = 2 [1.3]; 200 mg twice daily=8 [5.8]) and pelvic pain (ie, worsening of pelvic pain as reported by the investigator) in Elaris EM-IV (150 mg once daily n [%] = 3 [2.1]; 200 mg twice daily=3 [2.1]). Serious adverse events reported by more than one woman across both Elaris EM-III and Elaris EM-IV included endometriosis (n=4), appendicitis (n=3), abdominal pain (n=2), and back pain (n=2). During the 6-month extension study treatment period, the most commonly reported adverse event with new onset was urinary tract infection (Appendix 5, available online at http://links.lww.com/AOG/B100). The incidence of hot flushes with new onset was less than 5% in the 150-mg once-daily dose group and less than 8% at 200 mg twice daily; no women

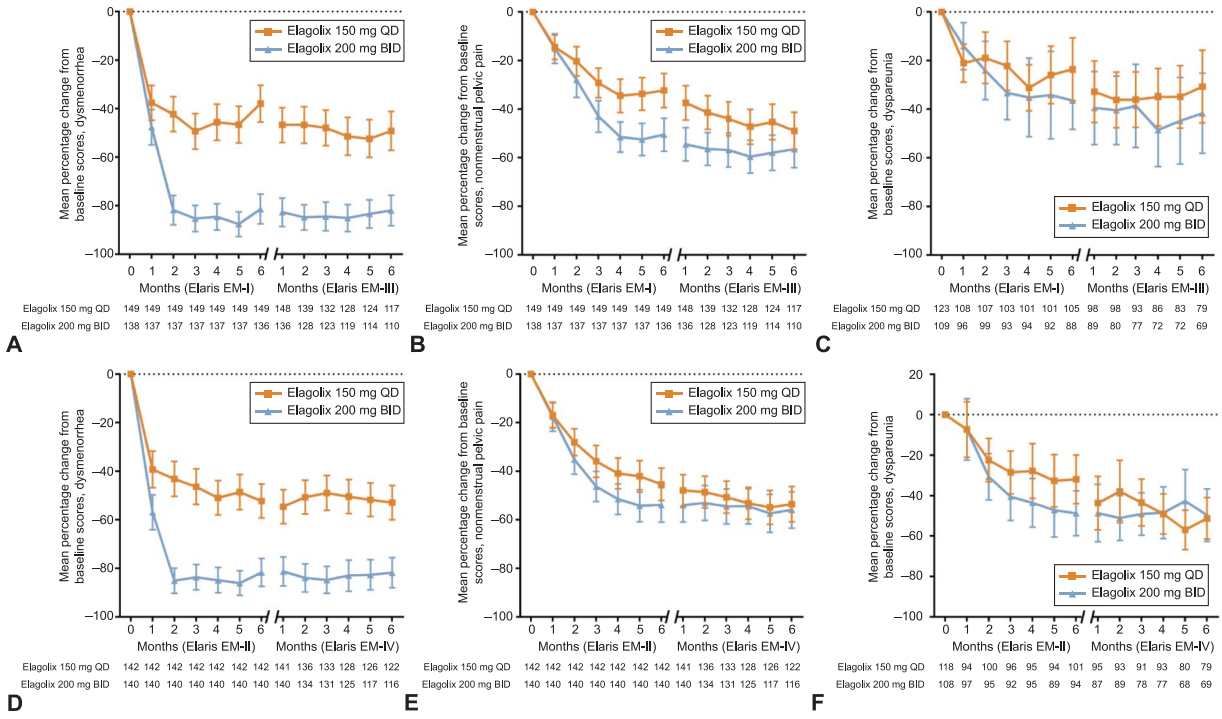

Fig. 2. Mean percent change from baseline in dysmenorrhea (**A** and **D**), nonmenstrual pelvic pain (**B** and **E**), and dyspareunia scores (**C** and **F**). *Error bars* represent 95% CIs. Between-group comparisons were not predefined and not performed. Months 1–6 in Elaris EM-I and Elaris EM-II are from women who enrolled in the extension studies. QD, once daily; BID, twice daily; EM, endometriosis.

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discontinued as a result of new-onset hot flush during the extension studies.

The most common reason for discontinuation was an adverse event (Elaris EM-III, 18 [6.3%]; Elaris EM-IV, 22 [7.8%]), with the most common being decreased BMD (greater than 8% decrease in BMD from baseline required study discontinuation per the study protocol) (Elaris EM-III: 150 mg once daily=1

Table 3. Top-Line Summary of Adverse Events Over the Course of 12 Months of Elagolix Treatment

	Elaris EM-III		Elaris EM-IV	
Adverse Event	Elagolix 150 mg QD (n=149)	Elagolix 200 mg BID (n=138)	Elagolix 150 mg QD (n=142)	Elagolix 200 mg BID (n=140)
Any	135 (90.6)	127 (92.0)	131 (92.3)	126 (90.0)
Any serious	6 (4.0)	6 (4.3)	11 (7.7)	9 (6.4)
Any severe	26 (17.4)	33 (23.9)	17 (12)	21 (15.0)
Any leading to discontinuation	6 (4.0)	12 (8.7)	8 (5.6)	13 (9.3)
Deaths	0	0	0	0
Most common in either study*				
Hot flush	44 (29.5)	72 (52.2)	36 (25.4)	77 (55.0)
Headache	29 (19.5)	35 (25.4)	31 (21.8)	41 (29.3)
Nausea	18 (12.1)	34 (24.6)	25 (17.6)	21 (15.0)
Urinary tract infection	26 (17.4)	16 (11.6)	15 (10.6)	19 (13.6)
Sinusitis	18 (12.1)	18 (13)	11 (7.7)	16 (11.4)
Arthralgia	7 (4.7)	11 (8)	13 (9.2)	18 (12.9)

QD, once daily; BID, twice daily.
Data are n (%).
* In descending order of elagolix treatment overall in Elaris EM-III, then Elaris EM-IV.

[0.7%], 200 mg twice daily=6 [4.3%]; Elaris EM-IV: 150 mg once daily=0 [0%]; 200 mg twice daily=4 [2.9%]).

After 12 months of elagolix treatment in Elaris EM-III, 83.3% of women in the 150-mg once-daily dose group (Elaris EM-IV=75.2%) and 42.6% in the 200-mg twice-daily dose group (Elaris EM-IV=39.4%) had an increase, no change, or decrease of 3% or less from baseline in lumbar spine BMD (Fig. 3); results were similar for total hip and femoral neck. After 12 months of treatment, the percentage of women who had a decrease from baseline greater than 5% in lumbar spine BMD was higher in the 200-mg twice-daily group than the 150-mg once-daily group in each study (Fig. 3). After 12 months of treatment in Elaris EM-III, the mean percent change from baseline in lumbar spine BMD was −0.63% for the 150-mg once-daily group (Elaris EM-IV=−1.10%) and −3.60% for the 200-mg twice-daily group (Elaris EM-IV=−3.91%) (Fig. 4).

No women in Elaris EM-III and one woman on the elagolix 200-mg twice-daily dose in Elaris EM-IV had a Z-score below −2.0, the lower bound of the normal age and race-matched range,[22] at any time in the studies in any measured anatomic region (Fig. 4; Appendix 6, available online at http://links.lww.com/AOG/B100). Within the population who had DXA scans during the posttreatment period of Elaris EM-IV, the median and quartile BMD Z-scores for the lumbar spine showed a trend of improvement in the 200-mg twice-daily group (Fig. 4).

Women who were treated with elagolix over 12 months had increases in the mean change from baseline in total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides; changes in the LDL: HDL ratio were less than 0.2 (Table 4). At 1 month posttreatment, the mean total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were less than 2 mg/dL above baseline levels or below (Table 4).

There were five pregnancies in the Elaris EM-III treatment period among women previously treated with elagolix. There were four normal live births at term and one pregnancy outcome was lost to follow-up. There were five pregnancies in Elaris EM-IV among patients previously treated with elagolix. One pregnancy occurred after the last dose of elagolix. This pregnancy resulted in a normal live birth at term. The infant was later diagnosed with a simple craniosynostosis without other associated findings. There was no evidence of fetal exposure to elagolix, because there was no elagolix detected in serum when tested before the date of conception, as dated by ultrasonography. For the other four pregnancies, three women elected termination of pregnancy, and one pregnancy outcome was lost to follow-up.

The majority (60% or greater) of women in each dose group and across studies had an endometrial thickness of less than 8 mm after 12 months of elagolix treatment (Table 4). There were numeric decreases from baseline in endometrial thickness after 12 months of treatment at 200 mg twice daily; women treated with elagolix 150 mg once daily had an apparent numeric increase from baseline in endometrial thickness after 12 months with greater than 60% less than 8 mm and greater than 90% less than 12 mm (Table 4; Appendix 7, available online at http://links.lww.com/AOG/B100). Endometrial histology from Elaris EM-III showed that a greater proportion of women had normal quiescent or minimally stimulated endometrium after 12 months of elagolix treatment compared with baseline; a smaller percentage of women in the 200-mg twice-daily dose group had proliferative endometrium after 12 months of elagolix treatment compared with baseline (Table 4).

After 12 months of treatment with elagolix 150 mg once daily, 27% of women in Elaris EM-III and 20% in Elaris EM-IV were amenorrheic (Appendix 7, http://links.lww.com/AOG/B100). After 12 months of continuous treatment with elagolix 200 mg twice daily, 63% in Elaris EM-III and 61% in Elaris EM-IV were amenorrheic (Appendix 7, http://links.lww.com/AOG/B100). The percentage of women within each elagolix dose group experiencing amenorrhea was similar during each month in the extension study treatment period (Appendix 7, http://links.lww.com/AOG/B100). In posttreatment month 1 of Elaris EM-III and EM-IV, respectively, 76% (95/125) and 78% (97/124) of women in the elagolix 150-mg once-daily groups and 57% (67/118) and 54% (65/121) of women in the elagolix 200-mg twice-daily groups had reported posttreatment menses. By 3 months posttreatment, more than 90% of women in both dose groups had reported posttreatment menses.

DISCUSSION

In two similar double-blind, phase 3 extension studies, responder rates among women with moderate to severe endometriosis-associated pain treated with elagolix 200 mg twice daily were approximately 75–78% for dysmenorrhea, 67–69% for nonmenstrual pelvic pain, and 58–60% for dyspareunia after 12 months of treatment. Although pain responder rates among women treated with elagolix 150 mg once daily were lower than the higher 200-mg twice-daily dose after 12 months of treatment, more

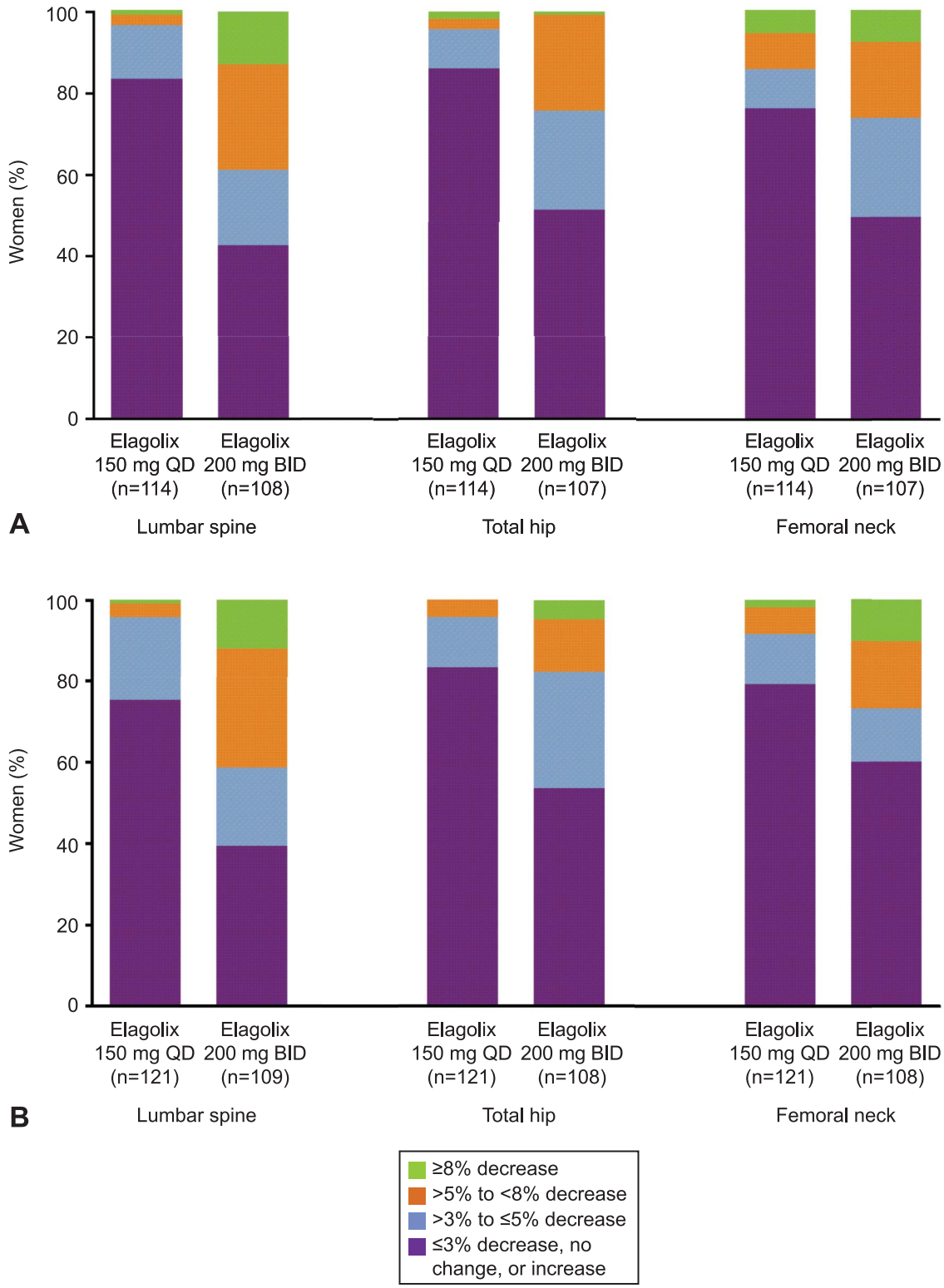

Fig. 3. Categorical mean percent change from baseline in bone mineral density after 12 months of elagolix treatment. Elaris EM-III (**A**) and Elaris EM-IV (**B**). Between-group comparisons were not predefined and not performed. QD, once daily; BID, twice daily.

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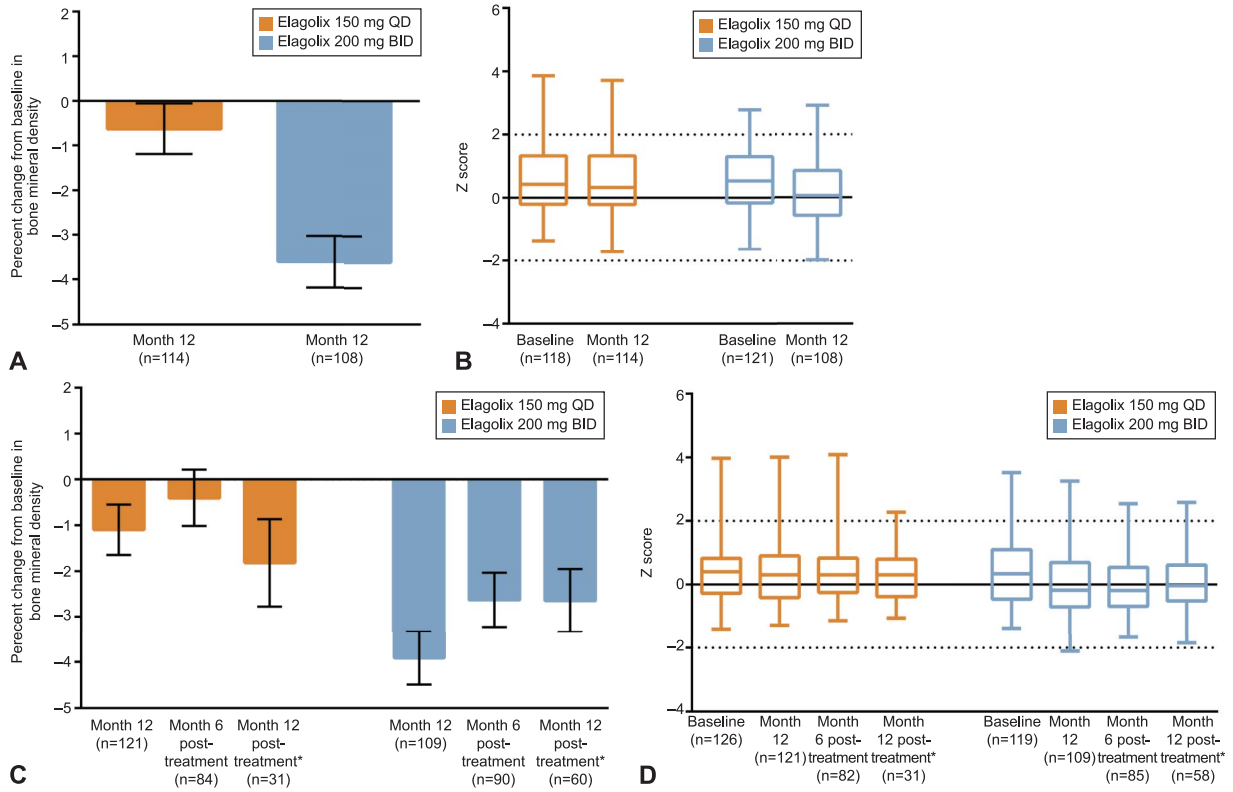

Fig. 4. Mean percent change from baseline in bone mineral density of the lumbar spine (**A** and **C**) and median, quartile 1, quartile 3, minimum, and maximum of lumbar spine bone mineral density Z scores (**B** and **D**) after 12 months of treatment in Elaris EM-III (**A** and **B**) and Elaris EM-IV (**C** and **D**) and at posttreatment months 6 and 12* (Elaris EM-IV only). Baseline was before dosing in the preceding double-blind, placebo-controlled trials (Elaris EM-I and Elaris EM-II). *Dotted lines* indicate the normal age- and race-matched range. Month 12 during the extension treatment period includes women who prematurely discontinued and women that had 12 months or greater of elagolix treatment as discussed in the Methods. For mean percent change from baseline, the error bars represent 95% CI. Between-group comparisons were not predefined and not performed. *Elaris EM-III was not designed to evaluate posttreatment bone mineral density recovery for all women. For Elaris EM-IV, all women were required to have a follow-up dual-energy X-ray absorptiometry (DXA) at 6 months posttreatment. However, only women who had a decrease greater than 1.5% from baseline in the lumbar spine or a decrease greater than 2.5% in total hip bone mineral density at 6 months posttreatment were required to have a follow-up DXA at 12 months posttreatment. QD, once daily; BID, twice daily; BL, baseline; EM, endometriosis.

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than 50% of the women demonstrated a clinically meaningful response in dysmenorrhea (approximately 52%) and nonmenstrual pelvic pain (approximately 67%) and approximately 45% had a clinically meaningful response in dyspareunia. These long-term responder rates are similar to those reported in the preceding Elaris EM-I and Elaris EM-II trials,[21] which demonstrates the sustained effect of elagolix for the treatment of endometriosis-associated pain. In parallel with reduction of pain symptoms, a majority of women demonstrated improved quality of life and a decrease from baseline in the use of rescue analgesic agents after 12 months of elagolix treatment (opioid use: greater than 30% mean reduction at 150 mg once daily, greater than 65% mean reduction at 200 mg twice daily).

Long-term elagolix treatment at both doses in the extension studies had anticipated changes as a result of decreased estradiol levels including reduced BMD, increases in lipid levels, and hot flushes. For most women, hot flush events began during the preceding Elaris EM-I and -II trials and continued into the extension studies. The overall incidence of hot flush across 12 months of elagolix treatment (30–55% of women across studies and doses) was lower than previous reports of treatment with leuprolide acetate alone (88% of women[23]) and comparable with hot flush rates experienced among women treated with leuprolide acetate with hormonal add-back therapy (40–58% of women[23]).

The BMD decreases observed after 12 months of elagolix treatment were numerically greater than

Table 4. Changes From Baseline in Plasma Lipids, Endometrial Thickness, and Endometrial Pathology After 12 Months of Elagolix Treatment

	Elaris EM-III		Elaris EM-IV	
	Elagolix 150 mg QD	Elagolix 200 mg BID	Elagolix 150 mg QD	Elagolix 200 mg BID
Plasma lipids after 12 mo of treatment (mg/dL)	n=115	n=106	n=118	n=113
Cholesterol	7.4±23.3	19.2±23.4	8.0±22.7	16.2±31.7
LDL cholesterol	3.7±20.7	12.7±20.2	5.9±19.3	10.6±28.1
HDL cholesterol	1.4±9.4	3.6±10.3	1.7±7.5	4.6±10.5
Triglycerides	17.0±77.5	14.3±51.5	1.7±58.4	6.4±60.3
LDL:HDL cholesterol*†	0.02±0.4	0.17±0.5	0.07±0.3	0.07±0.7
Plasma lipids posttreatment mo 1 (mg/dL)	n=120	n=110	n=110	n=115
Cholesterol	−1.13±20.1	0.02±21.0	−2.1±18.6	−3.1±25.2
LDL cholesterol	−1.43±17.0	0.73±17.3	−1.5±18.3	−2.9±21.9
HDL cholesterol	−0.18±8.3	−0.28±9.4	0.39±8.8	−0.13±8.6
Triglycerides	1.08±62.8	−2.13±39.6	−6.6±47.2	−2.3±49.3
LDL:HDL cholesterol	−0.01±0.4	0.06±0.5	−0.01±0.44	−0.06±0.48
Endometrial thickness (mm)	n=102	n=97	n=103	n=104
Baseline (mean)	6.8	6.4	6.3	6.5
Change from baseline to after 12 mo of treatment‡	0.6±3.8	−0.8±3.4	1.3±3.5	−0.5±4.0
Categorical endometrial thickness after 12 mo of treatment (mm)	n=102	n=97	n=103	n=104
Less than 8	64 (62.7)	83 (85.6)	62 (60.2)	81 (77.9)
8 to less than 12	29 (28.4)	10 (10.3)	34 (33.0)	19 (18.3)
12 to less than 18	9 (8.8)	4 (4.1)	7 (6.8)	4 (3.8)
18 or greater	0	0	0	0
Baseline biopsy results§	n=147	n=138		
Normal quiescent or minimally stimulated	6 (4.1)	2 (1.4)		
Proliferative	67 (45.6)	85 (61.6)		
Normal secretory, mixed, breakdown, menstrual	67 (45.6)	48 (34.8)		
Hyperplasia	1 (0.7)	0		
Polyp	2 (1.4)	0		
Insufficient tissue for diagnosis	1 (0.7)	2 (1.4)		
Women without biopsy results	2	0		
Biopsy results after 12 mo of elagolix treatment§	n=110	n=99		
Normal quiescent or minimally stimulated	14 (12.7)	50 (50.5)		
Proliferative	58 (52.7)	29 (29.3)		
Normal secretory, mixed, breakdown, menstrual	30 (27.3)	14 (14.1)		
Hyperplasia	0	0		
Polyp	1 (0.9)	0		
Insufficient tissue for diagnosis	6 (5.5)	6 (6.1)		
Women without biopsy results	39	39		

QD, once daily; BID, twice daily; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Data are mean±SD or n (%) unless otherwise specified.
Between-group comparisons were not predefined and not performed.
* Elaris EM-III: 150 mg QD n=113, 200 mg BID n=106.
† Elaris EM-IV: 150 mg QD n=116, 200 mg BID n=112.
‡ Endometrial thickness was measured by transvaginal ultrasonography at baseline (within 10 days of menses) in the preceding double-blind, placebo-controlled trials and after at least 12 35-day calendar months regardless of menstrual cycle.
§ Biopsies were conducted in Elaris EM-III and not in Elaris EM-IV.

the decreases observed after 6 months of elagolix treatment in the preceding double-blind, placebo-controlled trials and also greater at the 200-mg twice-daily elagolix dose. All women but one on the elagolix 200-mg twice-daily dose had a BMD Z-score of −2 or greater, within the normal age- and race-matched range, after 12 months of treatment.[22]

Loss of BMD have been observed with GnRH agonists (eg, leuprolide acetate); however, the magnitude of elagolix's effect on BMD at each dose was less compared with leuprolide acetate (6.3% mean decrease in lumbar spine BMD with after 12 months of leuprolide acetate alone).[23] Concomitant hormonal add-back therapy has been previously shown

to alleviate hypoestrogenic symptoms associated with GnRH agonist treatment and future studies are currently planned to assess the safety and efficacy of elagolix in combination with low-dose, add-back hormonal therapy in women with endometriosis-associated pain (NCT03213457 and NCT03343067). After cessation of treatment in Elaris EM-IV, BMD values returned toward baseline values during the posttreatment follow-up period with the steepest slope of recovery observed for women receiving elagolix 200 mg twice daily. It is important to note that posttreatment follow-up BMD data at 12 months were limited to women with the greatest decreases in BMD at the end of elagolix treatment, per the protocol, and therefore do not reflect the true rate of improvement in BMD 12 months off therapy. These data are also limited by the protocol requirement that women with significant BMD loss in the preceding double-blind, placebo-controlled trials (8% or greater BMD decrease in the spine, femoral neck, or total hip) were ineligible for extension study enrollment and therefore not included in the long-term estimation of BMD loss.

Elagolix treatment was associated with changes in the lipid profile that were first observed during Elaris EM-I and -II and no further increases were observed during the extension studies. All changes were small and included both favorable (increase in HDL) and unfavorable (increase in LDL and triglycerides) changes. The lipid profile returned to pretreatment levels within month 1 of the posttreatment follow-up period. This young female population was at low cardiovascular risk based on the American Heart Association online calculators and with less than 5 years of treatment is unlikely to have clinically important lipid changes that affect future cardiovascular risk; however, the precise risk remains unknown. In a small study, a GnRH agonist resulted in a similar shift in lipid levels with a mean increase in the LDL cholesterol level of 14.6 mg/dL and a mean increase in the HDL cholesterol level of 2.5 mg/dL after 12 months of treatment.[23]

There were no adverse endometrial changes after 12 months of elagolix treatment at both doses, suggesting that the antiproliferative effect of hypoestrogenism induced by elagolix in Elaris EM-I and -II was maintained long term. The small increase in endometrial thickness observed for women in the 150-mg once-daily treatment group is likely the result of the timing of transvaginal ultrasound assessment, which was measured at baseline early in the menstrual cycle at the endometrium's thinnest state, whereas the measurements at months 6 and 12 were not timed in the menstrual cycle.

Elaris EM-III and Elaris EM-IV were limited by the entry criteria. For example, women were required to have completed the preceding double-blind, placebo-controlled trials to enroll in the extension studies, resulting in a potential selection for women who responded to treatment. The absence of a placebo control in these extension studies also limits interpretation of the results. Additional limitations include the absence of long-term symptom recurrence data off therapy that the extension studies were not designed to evaluate efficacy and safety comparisons between doses. Despite these limitations, the treatment length, multiple dosing options, and the fact that pain responder rates were controlled for rescue analgesia use are strengths of these extension studies.

The efficacy and safety of elagolix treatment over the course of 12 months were consistent with its estrogen-suppressing mechanism of action and the previously published 6-month treatment results from the preceding double-blind, placebo-controlled Elaris EM-I and Elaris EM-II trials.[21] Elagolix treatment at both doses was associated with decreases in BMD, suggesting that a DXA evaluation at 12 months would be of clinical value to identify those women who might be at risk for falling outside the normal Z-score range with continued therapy. Overall the extension studies show sustained efficacy without new or unexpected adverse effects and suggest that administration of elagolix may be safely and effectively prolonged in an appropriately selected population of patients with symptomatic endometriosis.

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