


Elagolix Treatment for Endometriosis-Associated Pain: Results from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study

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Abstract

This Phase 2 study evaluated the safety and efficacy of elagolix for treating endometriosis-associated pain. A total of 155 women with laparoscopically confirmed endometriosis were randomized to placebo, elagolix 150 mg, or elagolix 250 mg once daily for 12 weeks. Placebo patients were rerandomized to elagolix and elagolix patients continued their dosing assignment for 12 additional weeks; the primary efficacy measure was changed from baseline in the monthly mean numerical rating scale for pain at week 12. Monthly mean (standard error of the mean) reductions were greater with elagolix versus placebo (-1.19 ± 0.18 , -1.25 ± 0.18 , and -0.88 ± 0.18 for elagolix 150 mg, 250 mg, and placebo, respectively); differences were not statistically significant. Monthly mean dysmenorrhea and nonmenstrual pelvic pain scores were reduced with elagolix, with significant differences for dysmenorrhea at weeks 8 and 12 versus placebo ($P < .05$). Minimal bone mineral density changes were observed with elagolix treatment. In women with endometriosis-associated pain, elagolix demonstrated an acceptable efficacy and safety profile in this Phase 2 study.

Keywords

GnRH antagonist, endometriosis, elagolix

Introduction

Endometriosis is a chronic, progressive disease that is prevalent in women of reproductive age.¹ Women with endometriosis frequently experience chronic pelvic pain, although the type and severity of pain vary among patients and do not correlate with the laparoscopic stages of the disease.²⁻⁴ This heterogeneity of the observed pain symptoms contributes to the difficulty in diagnosing endometriosis.⁵⁻⁷ As a result, there can be long diagnostic delays, with the average time to diagnosis of endometriosis being more than 9 years after the initial onset of pain symptoms.⁸

Despite the availability of medical and surgical therapies, an effective and well-tolerated treatment of endometriosis remains a largely unmet medical need. Oral contraceptives (OCs), although not approved for the treatment of endometriosis-associated pain, are often used as first-line therapy. However, over time many women on OCs no longer have adequate pain relief and require second-line therapy.^{6,9,10} Progestin monotherapy can be efficacious for the reduction in endometriosis-associated pain but is often associated with breakthrough bleeding, alterations in mood, weight gain, and breast tenderness.¹¹⁻¹³ Second-line therapies with proven efficacy for the treatment of

endometriosis-associated pain are often limited by undesirable side effects. For example, danazol is limited by weight gain and androgenic side effects.¹⁴ Gonadotropin-releasing hormone (GnRH) agonists completely suppress hormonal production; thus, their long-term use is limited by hypoestrogenic effects, including bone loss.¹⁵ The addition of hormonal add-back therapy to GnRH agonists reduces hypoestrogenic effects,¹⁶ but for reasons that are unclear, only one-third of the women taking GnRH agonists are also prescribed add-back therapy.¹⁷

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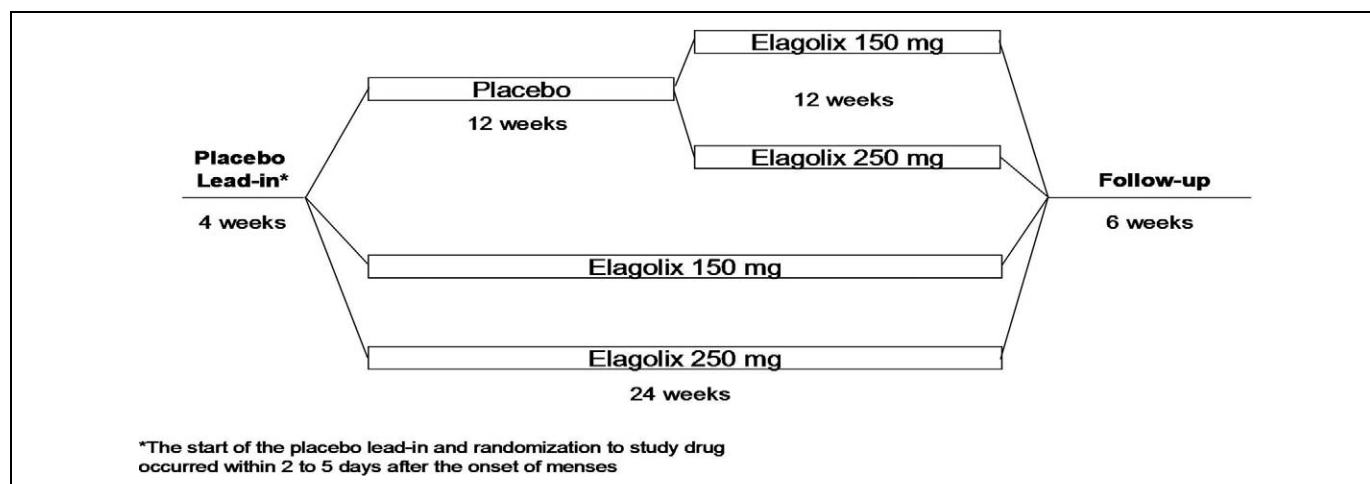


Figure 1. Study design.

For many women, current medical therapies are inadequate, and surgery for the excision and/or ablation of endometriosis lesions is common. Even after surgical intervention, pain recurrence affects 20% to 56% of the patients over 5 years of follow-up, with a high likelihood of postoperative adhesion development.^{18,19} Treatments that are safe, well tolerated, and efficacious for long-term therapy of endometriosis are therefore needed.

Elagolix is an oral short-acting, nonpeptide, GnRH antagonist that unlike injectable GnRH analogs produces a dose-dependent suppression of pituitary and ovarian hormones in women, that is from partial ovarian suppression at lower doses to full suppression at higher doses. Results from a recent phase 2 study are reported herein.

Materials and Methods

Study design

This randomized, multicenter, double-blind, placebo-controlled, parallel group study examined the safety and efficacy of 2 doses of elagolix (150 mg and 250 mg) taken once daily. The study was conducted at 50 US centers from February 2008 to August 2009 and included up to 8 weeks of screening with approximately 4 weeks of a single-blind placebo lead-in period. Both the start of the placebo lead-in period and randomization to double-blind study drug occurred within 2 to 5 days of the onset of menses. At the end of the placebo lead-in period, baseline assessments were collected and patients were randomized (1:1:1) to elagolix 150 mg, elagolix 250 mg, or placebo for an initial 12-week treatment period (Figure 1). At the end of week 12, patients on placebo were rerandomized to one of the elagolix treatment groups, while patients on elagolix continued their treatment assignment for an additional 12 weeks (Figure 1). A follow-up visit was conducted approximately 6 weeks after completion of the 24-week treatment period. All patients provided informed consent, and the study protocol was approved by a central institutional review board (Schulman Institutional Review Board [IRB]) or a site's local IRB and was

conducted in accordance with Good Clinical Practice²⁰ and the Declaration of Helsinki.

Randomization and Blinding

After screening, an interactive voice response system was used to randomize patients in a 1:1:1 ratio to receive elagolix 150 mg, elagolix 250 mg, or matching placebo for 12 weeks and to rerandomize patients who initially received placebo to elagolix 150 mg or elagolix 250 mg at week 12. Blinding was achieved using a double-dummy design with all patients receiving elagolix and/or matching placebo as 2 identical tablets. Patients, the investigator, sponsor, and all study personnel were blinded to all treatments administered to the patients.

Patients

Eligible patients were women aged 18 to 49 years, with diagnosis of endometriosis by laparoscopic visualization within 8 years of screening. Randomized patients had a total composite pelvic signs and symptoms score (CPSSS) ≥ 6 at screening (using a Biberoglu and Behrman scale²¹) and scores of at least moderate (≥ 2) for dysmenorrhea and at least mild (≥ 1) for nonmenstrual pelvic pain at baseline. Randomized patients also agreed to use 2 forms of nonhormonal contraception (eg, condom with spermicide) during the study.

Patients were excluded if they were administered a GnRH agonist, a GnRH antagonist, or danazol within 6 months of screening, depot medroxyprogesterone acetate within 3 months of screening, or had used hormonal contraception or other hormonal therapy within 1 month of screening. Patients were also excluded if they had a history of unresponsiveness to GnRH agonist or antagonist therapy or if they had surgical treatment for endometriosis within 1 month of the start of screening.

Efficacy Measures

Efficacy measures included the daily assessment of pelvic pain using the 11-point numerical rating scale (NRS) and

assessment of dysmenorrhea and nonmenstrual pelvic pain using a 4-point Biberoglu and Behrman scale²¹ (0 = none, 1 = mild, 2 = moderate, and 3 = severe) that was modified for daily collection of dysmenorrhea and nonmenstrual pain assessments. Assessments occurred at approximately the same time each day using an electronic diary (e-Diary) that was also used to record daily use of analgesics for endometriosis-associated pain. Additional efficacy assessments included the dyspareunia component of the CPSSS and the Patient Global Impression of Change (PGIC),²² which were completed at baseline and at the end of weeks 4, 8, 12, 16, 20, 24, and at the week 30 follow-up visit (or early termination). Concurrently, quality of life was assessed using the Endometriosis Health Profile 5 (EHP-5)²³ core questionnaire containing 5 domains.

Use of Analgesics

Mild analgesics (eg, naproxen, celecoxib, ibuprofen, mefenamic acid, and acetaminophen) and strong analgesics (eg, hydrocodone/acetaminophen and codeine/acetaminophen and hydrocodone/ketorolac) were permitted on an “as needed” basis and were documented by the patients in their e-Diaries. The use of analgesics with a long half-life (eg, controlled-release oxycodone) and the use of prophylactic analgesics were prohibited.

Hormone Concentrations

Blood samples to determine estradiol concentrations were collected at baseline, at the end of weeks 4, 8, 12, 16, 20, and 24, and at the week 30 follow-up visit (or early termination). Estradiol concentrations were determined by liquid chromatography with tandem mass spectrometry performed by a central laboratory (Celerion; Lincoln, Nebraska). The lower limit of quantitation was 2.5 pg/mL, the interday precision was $\leq 5.7\%$, and the accuracy ranged from -2.8% to 1.7% .

Safety

The incidence and severity of adverse events were recorded throughout the study. Patients used their e-Diaries to record the number of hot flashes experienced daily and the intensity of the worst hot flash experienced since the last entry. Standard clinical laboratory assessments were performed by a central laboratory (ICON Laboratories, Farmingdale, New York).

Bone mineral density (BMD) of the spine and total femur was measured by dual energy x-ray absorptiometry (DXA) at screening and at the end of weeks 12 and 24 and analyzed by a central laboratory (Bio-Imaging Technologies, Newtown, Pennsylvania). If a patient's BMD at the end of week 24 decreased more than 3% from baseline, the patient was required to have an additional DXA scan at 6 months posttreatment. The bone resorption biomarker, serum N-telopeptide, was assessed at weeks 12, 24, and 30 by an enzyme-linked immunosorbent assay (provided by ICON laboratories, Farmingdale, New York).

Patients daily recorded the occurrence and the intensity of uterine bleeding in their e-Diaries from screening through the

follow-up visit using the following guidelines: light = spotting, moderate = normal flow, and heavy = heavy flow with flooding and/or clotting.

Statistical Analysis

The planned sample size of 150 patients (50 per group) was expected to provide 84% power to detect a difference of 1.5 units between elagolix and placebo for the change from baseline in the monthly mean NRS at week 12. This power calculation was based on a standard 2-sided, 2-sample *t* test at the .05 level of significance and with an assumed common standard deviation (SD) of 2.5 units (a “unit” difference corresponded to a difference of one category on the NRS). The SD estimate was based on results from a previous phase 2 study for the change from baseline in the monthly mean visual analog scale (VAS).

The safety analysis included all patients who received at least 1 dose of study drug. The intent-to-treat analysis set was used for efficacy analyses and included all randomized patients who received at least 1 dose of study drug and reported at least 10 NRS values during the initial 12-week treatment period.

Descriptive statistics were calculated for the monthly (1 month was equal to the time between scheduled visits) mean scores of the daily NRS, dysmenorrhea, and nonmenstrual pelvic pain scores, as well as for dyspareunia, the monthly percentage of days with analgesic use, and responses to the EHP-5. Changes from baseline in these assessments were analyzed by a repeated measures analysis of covariance model. The model included fixed effects for treatment, time, the treatment-by-time interaction, a random effect for subject, and the baseline-by-time interaction, and the baseline value as a covariate. Descriptive statistics were calculated for PGIC scores, and comparisons between treatment group mean scores were performed using a repeated measures 1-way analysis of variance.

Results

A total of 155 patients were randomized, and 102 patients completed the study (Figure 2). Overall, a higher percentage of patients who were initially randomized to elagolix completed both treatment periods of the study. Patient demographics and baseline characteristics were similar among the 3 treatment groups (Table 1).

Endometriosis Pain Assessments

At baseline (average of all daily values during the placebo lead-in period), monthly mean (standard error of the mean [SEM]) endometriosis-associated pain as measured by NRS was similar in all 3 groups (Figure 3). Reductions in monthly mean NRS were observed in all 3 treatment groups at weeks 4, 8, and 12 (Figure 3). The reductions were numerically greater with elagolix treatment compared with placebo at week 12 (-1.19 ± 0.18 , -1.25 ± 0.18 , and -0.88 ± 0.18 for elagolix 150 mg,

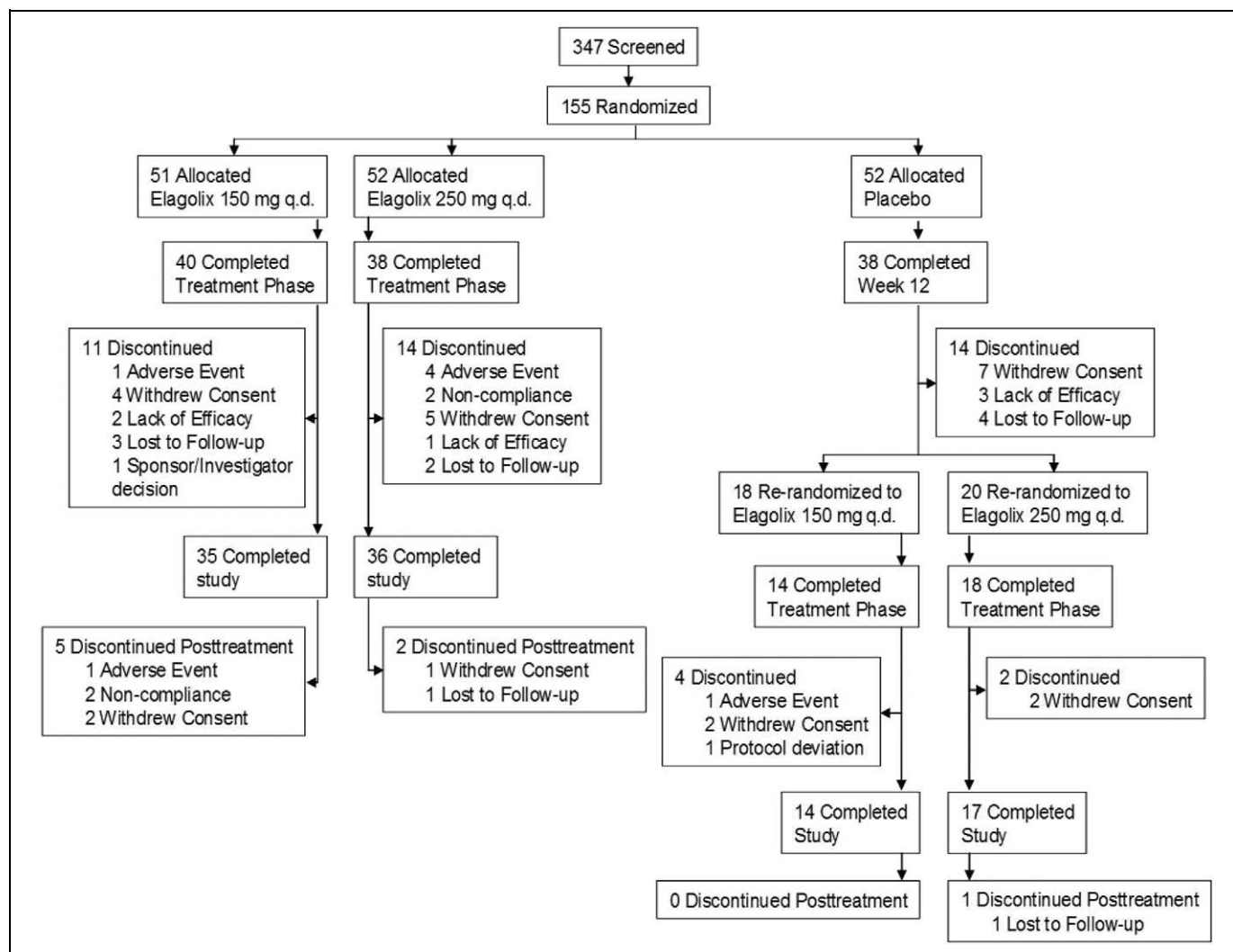


Figure 2. Flow of patients through the trial.

250 mg, and placebo, respectively) but the differences did not reach statistical significance. During weeks 13 to 24, there continued to be further reductions from baseline.

For dysmenorrhea and nonmenstrual pelvic pain measured by a modified Biberoglu and Behrman scale, the monthly mean scores were reduced through week 12 in all 3 treatment groups (Figure 4A and B). At week 12, the decreases in dysmenorrhea for both the elagolix treatment groups, 150 mg and 250 mg, were significantly larger compared with placebo ($P = .0021$ and $P = .0003$, respectively), whereas the decreases in nonmenstrual pelvic pain for both the elagolix treatment groups were numerically larger than for the placebo group but not significant. The reductions in monthly mean dysmenorrhea and nonmenstrual pelvic pain scores were maintained through weeks 13 to 24.

Dyspareunia scores were similar at baseline and were reduced through week 12 in all 3 treatment groups (Figure 5). Mean reductions were significantly greater for elagolix 150 mg compared with placebo at weeks 8 and 12 ($P = .0025$ and $P = .0316$, respectively) and for elagolix 250 mg compared with

placebo at weeks 4 and 8 ($P = .0392$ and $P = .0075$, respectively). Reductions in dyspareunia scores continued to be observed during weeks 13 to 24 and were comparable to the reductions observed with elagolix treatment during weeks 1 to 12.

During the placebo lead-in period, the percentage of days with prescription analgesic use was comparable in patients randomized to placebo and elagolix 150 mg but slightly lower in the elagolix 250 mg group (10%, 10%, and 7%, respectively). During the first 12 weeks of treatment, prescription analgesic use showed a modest decrease from baseline in all treatment groups, but the mean (SEM) reductions were slightly greater with elagolix treatment (-2.1 ± 1.6 , -2.6 ± 1.6 , and -3.3 ± 1.6 for placebo, elagolix 150 mg, and elagolix 250 mg, respectively; $P = .026$ for elagolix 250 mg vs placebo). During weeks 13 to 24, the percentage of days with prescription analgesic use continued to be reduced from baseline in all the treatment groups.

Patient global impression of change scores ranged from 3.7 to 3.9 at the end of the placebo lead-in period, corresponding to “no change” or “minimal improvement.” On treatment, mean

Table 1. Baseline Characteristics and Patient Demographics.

Characteristic	Placebo, N = 52	Elagolix 150 mg, N = 51	Elagolix 250 mg, N = 52
Age, years; mean (SEM)	31.2 (1.0)	30.9 (1.0)	31.0 (1.0)
Race, n (%)			
Caucasian	43 (82.7%)	42 (82.4%)	41 (78.8%)
Black	4 (7.7%)	4 (7.8%)	3 (5.8%)
Hispanic	3 (5.8%)	4 (7.8%)	6 (11.5%)
Other	2 (3.8%)	1 (2.0%)	2 (3.8%)
Weight, kg; mean (SEM)	72.2 (2.1)	74.1 (2.3)	74.4 (2.3)
Body mass index, kg/m ² ; mean (SEM)	26.7 (0.7)	27.3 (0.7)	27.3 (0.8)
Stage of endometriosis ^{a,b} , n (%)			
I	19 (36.5%)	12 (23.5%)	9 (17.3%)
II	11 (21.2%)	17 (33.3%)	20 (38.5%)
III	13 (25.0%)	11 (21.6%)	10 (19.2%)
IV	1 (1.9%)	4 (7.8%)	5 (9.6%)
Unknown	8 (15.4%)	7 (13.7%)	8 (15.4%)
Depth of endometriosis ^b , n (%)			
Superficial	25 (48.1%)	30 (58.8%)	29 (55.8%)
Infiltrative	8 (15.4%)	5 (9.8%)	9 (17.3%)
Unknown	19 (36.5%)	16 (31.4%)	14 (26.9%)
Months since diagnosis of endometriosis ^c , mean (SEM)	50.4 (6.2)	72.3 (8.6)	61.6 (8.0)
Months since last laparoscopy ^c , mean (SEM)	38.0 (4.2)	43.0 (4.9)	49.0 (4.8)

Abbreviation: SEM, standard error of the mean.

^a Stages of endometriosis, I: minimal, few, or superficial implants are evident; II: mild, more implants, and deeper involvement; III: moderate, more implants, with ovaries affected, and the presence of adhesions; IV: severe, as stage III, but with multiple and more dense adhesions (according to revised American Society for Reproductive Medicine endometriosis classification).

^b Stage and depth of endometriosis are based on evaluation at the time of laparoscopy not at baseline.

^c Number of months relative to the date of informed consent.

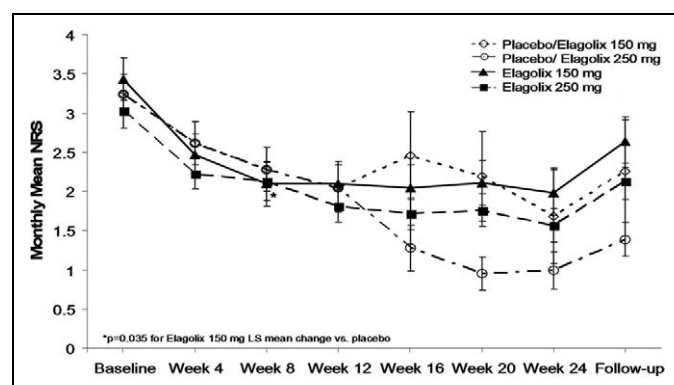


Figure 3. Monthly mean (standard error of the mean) endometriosis pain using the numeric rating scale.

(SEM) PGIC scores improved in all treatment groups. At week 12, mean PGIC scores were 2.2 ± 0.2 in both elagolix treatment groups, corresponding to “much improved,” compared with 3.2 ± 0.2 in the placebo treatment group, corresponding to “minimal improvement” ($P < .0001$ and $P = .0002$ for elagolix 150 mg and 250 mg vs placebo, respectively). During weeks 13 to 24, PGIC scores corresponding to “much improved” were observed in both the elagolix treatment groups.

Quality of Life

Changes in quality of life during treatment were assessed using the EHP-5. There were improvements with all 3 treatments in

all 5 domains of the EHP-5 assessing pain, control and powerlessness, emotional well being, social support, and self-image. In general, the greatest improvements were observed in the elagolix 150 mg group. At week 12, the pain dimension mean (SEM) change from baseline was -11.9 ± 3.3 , -23.1 ± 3.0 , and -19.2 ± 3.1 for the placebo, elagolix 150 mg, and elagolix 250 mg groups, respectively ($P = .0126$ for elagolix 150 mg vs placebo; $P = .1071$ for elagolix 250 mg vs placebo). At week 24, the mean (SEM) pain dimension score reductions were -25.7 ± 3.2 and -23.6 ± 3.7 for patients initially randomized to elagolix 150 mg and 250 mg, respectively.

Safety

Elagolix demonstrated an acceptable safety profile during the study. Adverse events that occurred in $\geq 5\%$ of patients are shown in Table 2. The adverse events that occurred more commonly in elagolix treatment groups compared with placebo were headache (1.9%, 9.8%, and 7.7% for the placebo, elagolix 150 mg, and elagolix 250 mg groups, respectively), nausea (1.9%, 9.8%, and 5.8%), and anxiety (0%, 5.9%, and 5.8%). Overall, 7 patients discontinued from the study due to an adverse event; 1 patient initially on placebo and then rerandomized to elagolix 150 mg (during elagolix treatment due to hot flush), 2 patients on elagolix 150 mg (one during treatment due to headache and nausea and one during posttreatment due to pelvic pain), and 4 patients on elagolix 250 mg (all during treatment; one patient each due to diabetes mellitus, menorrhagia,

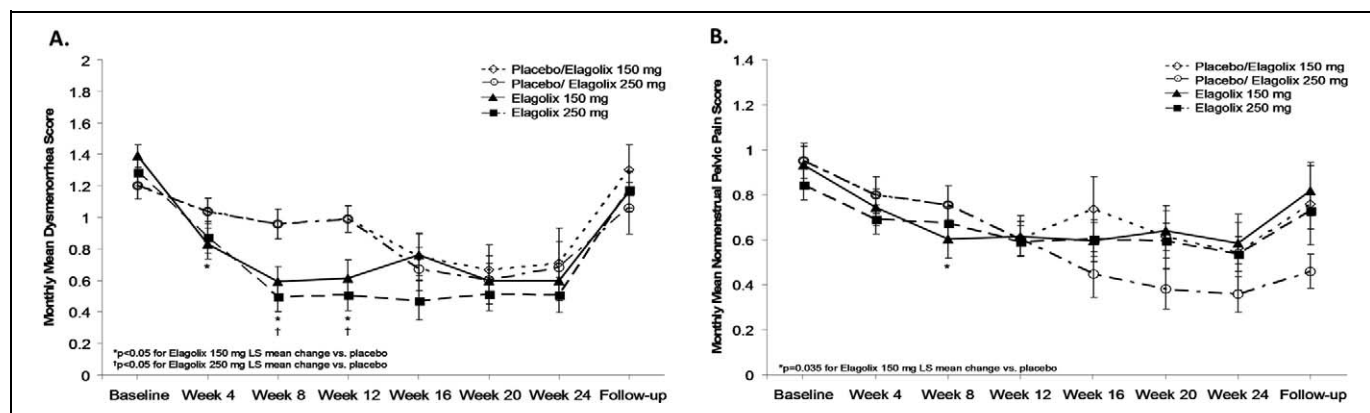


Figure 4. Monthly mean (standard error of the mean) dysmenorrhea (A) and nonmenstrual pelvic pain (B).

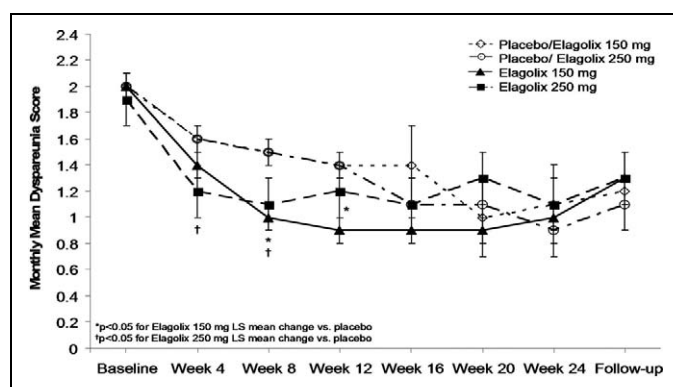


Figure 5. Monthly mean (standard error of the mean) dyspareunia score.

migraine, and pelvic pain). There were no deaths during the study, and serious adverse events were experienced by 3 patients. One patient in the elagolix 150 mg group experienced a serious adverse event of pelvic pain during the posttreatment period that the investigator judged as unlikely to be related to study drug.

There were 2 pregnancies during the study which occurred during the treatment period. One patient in the elagolix 250 mg group experienced a spontaneous abortion that was considered not related to study drug by the investigator, and 1 patient in the elagolix 150 mg group delivered an infant with a tracheoesophageal fistula that was judged by the investigator to be unlikely related to study drug.

Hot flashes were recorded daily using an e-Diary. During the placebo lead-in period, hot flashes were reported by 76.9%, 62.7%, and 51.9% of patients who were subsequently randomized to placebo, elagolix 150 mg, and elagolix 250 mg, respectively. During the treatment phase (weeks 1-12 for the placebo group and weeks 1-24 for the elagolix groups), hot flashes increased in all 3 treatment groups compared with the placebo lead-in (84.6%, 92.2%, and 86.3% in the placebo, elagolix 150 mg group, and elagolix 250 mg group, respectively). Overall, the median number of hot flashes per day was slightly larger in the elagolix treatment groups (0.30 and 0.28 for

elagolix 150 mg and 250 mg, respectively) compared with placebo (0.15). The majority of hot flashes recorded during the study were mild to moderate in intensity; only 1 patient randomized to placebo and rerandomized to elagolix 150 mg discontinued due to hot flash.

Bone Mineral Density

At week 12, there were slight decreases from baseline in spinal BMD in the elagolix treatment groups (mean [SD] percent changes of -0.045 ± 2.09 and -0.937 ± 2.75 for elagolix 150 mg and 250 mg, respectively) compared with an increase in the placebo treatment group (0.375 ± 2.10). At week 24, mean (SD) percentage decreases at the spine were -1.032 ± 1.98 and -1.631 ± 2.87 for elagolix 150 mg and 250 mg, respectively. At the femur, BMD was decreased at week 12 in all the groups (mean [SD] percentage changes from baseline of -0.283 ± 1.85 , -0.294 ± 1.76 , and -0.382 ± 1.34 for placebo, elagolix 150 mg, and 250 mg; respectively). At week 24, mean (SD) percentage changes at the femur were -0.743 ± 1.88 and -1.024 ± 1.76 for elagolix 150 mg and 250 mg, respectively. Overall, the changes were significant ($P < .05$) at the spine at week 12 for the 250 mg group and at the spine and femur at week 24 for both the 150 mg and the 250 mg doses. The BMD at week 24 had decreased more than 3% in 21 patients, and those patients had repeat DXA scans at week 48 (7 on elagolix 150 mg, 11 on elagolix 250 mg, 2 on placebo and rerandomized to elagolix 150 mg, and 1 on placebo and rerandomized to elagolix 250 mg). The BMD at week 48, in these patients, had generally increased slightly or remained similar to the week 24 measurement.

N-Telopeptide remained largely unchanged throughout the study. At week 12, the mean (SEM) change from baseline in N-telopeptide was -0.66 ± 0.46 nM BCE, -0.41 ± 0.36 nM BCE, and 0.22 ± 0.33 nM BCE for placebo, elagolix 150 mg, and elagolix 250 mg, respectively. At week 24, the mean (SEM) change from baseline in N-telopeptide was -1.07 ± 1.44 and -0.11 ± 0.46 for elagolix 150 mg and 250 mg, respectively.

Table 2. Adverse Events in $\geq 5\%$ of the Patients.

Adverse Event	Placebo, N = 52	Elagolix 150 mg, N = 51	Elagolix 250 mg, N = 52
Adverse events during treatment weeks 1-12			
Acne	1 (1.9%)	0	5 (9.6%)
Headache	1 (1.9%)	5 (9.8%)	4 (7.7%)
Vaginal mycosis	3 (5.8%)	0	4 (7.7%)
Nausea	1 (1.9%)	5 (9.8%)	3 (5.8%)
Urinary tract infection	2 (3.8%)	3 (5.9%)	3 (5.8%)
Anxiety	0	3 (5.9%)	3 (5.8%)
Adverse events for all patients who received elagolix during weeks 1-24			
Nausea		6 (8.7%)	6 (8.3%)
Vaginal mycosis		1 (1.4%)	6 (8.3%)
Acne		0	6 (8.3%)
Arthralgia		3 (4.3%)	5 (6.9%)
Headache		6 (8.7%)	4 (5.6%)
Upper respiratory tract infection		6 (8.7%)	4 (5.6%)
Urinary tract infection		5 (7.2%)	4 (5.6%)
Migraine		3 (4.3%)	4 (5.6%)

Estradiol Concentration

Patients were randomized on day 2 to 5 of their menses, and the baseline median (first quartile and third quartile) estradiol levels were comparable in all 3 treatment groups (33.0 [25.5, 52.4] pg/mL, 32.1 [21.1, 47.0] pg/mL, and 31.6 [26.2, 50.1] pg/mL for placebo, elagolix 150 mg, and 250 mg, respectively). At week 8, median estradiol values were 57.0 (32.5, 98.3) pg/mL, 35.8 (15.4, 50.0) pg/mL, and 32.6 (13.5, 56.8) pg/mL for the placebo, elagolix 150 mg, and 250 mg groups, respectively. At week 12, estradiol levels further increased to 65.0 (35.5, 120.0) pg/mL in the placebo group but remained unchanged in the elagolix treatment groups, 30.3 (17.8, 64.1) pg/mL and 30.9 (15.6, 49.4) pg/mL in the elagolix 150 mg and 250 mg groups, respectively. During weeks 16 to 24, estradiol concentrations remained similar to those observed in the elagolix 150 mg and 250 mg groups during weeks 1 to 12.

Uterine Bleeding

During the placebo lead-in period, the mean percentage of days with any uterine bleeding was similar among all treatment groups (22.6%, 24.3%, and 21.6% for placebo, elagolix 150 mg, and elagolix 250 mg, respectively). In the placebo treatment group, the mean percentage of days with any uterine bleeding remained unchanged during weeks 1 to 12. In the elagolix treatment groups, the mean percentage of days with any uterine bleeding was reduced to 15% for the elagolix 150 mg group and 14% for the elagolix 250 mg group during the treatment phase (weeks 1-24). In placebo patients who were rerandomized to elagolix treatment, the mean percentage of days with any bleeding was approximately 23% during weeks 1 to 12 and approximately 17% in both the groups after receiving elagolix treatment during weeks 13 to 24. The overall reduction in bleeding with elagolix treatment was primarily due to reductions in the mean percentage of days with moderate or heavy bleeding. Throughout the study, elagolix treatment led to

prolonged but regular menstrual cycles with a low incidence of breakthrough bleeding. After cessation of treatment, the mean (SEM) number of days to the first posttreatment menses was 19.6 ± 2.5 , 22.2 ± 2.7 , 21.6 ± 1.8 , and 23.7 ± 1.4 days in placebo patients rerandomized to 150 mg, placebo patients rerandomized to 250 mg, initially randomized to elagolix 150 mg, and initially randomized to elagolix 250 mg; respectively.

Discussion

Treatment with elagolix reduced endometriosis-associated pain during the 24-week treatment period. However, not all pain parameters reached statistical significance compared with placebo, and the placebo effect did not appear to be diminished by the inclusion of a 4-week placebo lead-in period. For the primary end point of the study (change from baseline in the monthly mean value of the daily NRS for endometriosis pain at week 12), larger reductions from baseline were observed for both the elagolix treatment groups compared with placebo; however, the differences were not statistically significant. The use of rescue analgesics was relatively low during screening and continued to decrease during the study, indicating that the reduction in pain scores from baseline was not driven by analgesic use.

Although there appears to be an increase in NRS measured pain after the initiation of elagolix 150 mg therapy, this is a result of splitting the placebo patients into 2 groups for rerandomization to elagolix therapy. When the subset of placebo patients who were subsequently randomized to elagolix 150 mg therapy were examined, their monthly mean NRS scores from week 12 to week 16, after randomization to elagolix 150 mg, were relatively flat. Similar to the NRS, monthly mean scores for dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia decreased from baseline in all treatment groups through week 12. There were statistically significantly greater reductions from baseline in dysmenorrhea and dyspareunia scores in the elagolix treatment groups compared with placebo

during the first 12 weeks of treatment. More patients initially randomized to elagolix completed the study, which may indicate greater satisfaction with the treatment they received. Additionally, patients receiving elagolix had PGIC scores corresponding to “much improvement” throughout the study.

Elagolix showed an acceptable safety and tolerability profile in this study. Treatment-related adverse events were generally mild to moderate in severity and were consistent with the drug’s mechanism of action.²⁴ Both BMD and estradiol concentrations were measured in the study. Estradiol concentrations remained in the low normal midfollicular range during treatment with both doses of elagolix, indicating partial estradiol suppression at these doses. As was expected when estradiol concentrations were maintained in this range, BMD showed only small changes over 24 weeks of treatment (spine -1.032% and -1.631% elagolix 150 mg and 250 mg, respectively). Furthermore, the reduction in BMD was much lower than the approximate 3% loss observed with 3 months of treatment with the GnRH agonist, leuprolide acetate.^{25,26}

Patients who received elagolix continued to have regular menstrual cycles during treatment; however, their cycles were prolonged and the number of days with bleeding per cycle was reduced. A limitation of the study was that although patients initiated dosing within 2 to 5 days after the onset of menses, the prolongation of cycle length in the elagolix groups prevented the synchronized measurement of estradiol levels throughout the study. In addition, they experienced little breakthrough bleeding and spotting and fewer days of moderate to heavy bleeding, which are common complaints with progestin therapy.^{11–13} Resumption of menses was rapid after elagolix discontinuation, which is a major consideration for women of reproductive age who may desire pregnancy.

Overall, the incidence of hot flash increased in all groups during the treatment period. Hot flashes were slightly increased with elagolix compared with placebo; however, most episodes were mild to moderate. The overall incidence of hot flash reported in the study was high in all the groups, including placebo, and may be the result of the method of collecting these events (rigorous daily assessment using the e-Diary).

Despite the protocol requirement for use of dual nonhormonal contraception, there were 2 pregnancies that occurred during the treatment period of this study, in both the elagolix treatment arms, with 1 of the pregnancy outcomes resulting in a tracheoesophageal fistula. An extensive review (eg, timing of elagolix exposure relative to organogenesis, type of abnormality, etc) of this congenital abnormality suggests that it is unlikely to be related to elagolix.

A review of all the data from the early clinical development program of elagolix to date estimates an annualized pregnancy rate of $\sim 3\%$ to 5% for the 250 mg dose and 150 mg dose every day, respectively (AbbVie data on file). Preclinical studies with elagolix have revealed no teratogenic effects at all doses studied (30 to $98 \times$ the clinically relevant dose; AbbVie data on file).

Despite the inclusion criteria of surgically confirmed endometriosis and a CPSSS score of ≥ 6 , most patients had

relatively low pelvic NRS pain scores reported during the placebo lead-in period, which was a limitation of the study. The baseline scores and those reported throughout the study corresponded with mild to moderate pain. The wording of the daily diary questions used in the study was not generally consistent with the CPSSS scores. For example, 62% of patients reported moderate or severe nonmenstrual pain at baseline using the nonmenstrual pelvic pain component of the monthly CPSSS. In contrast, the same patients reported 80% of the same nonmenstrual days as “none” or “mild” using the daily nonmenstrual pelvic pain scale during the placebo lead-in period. The mean daily nonmenstrual pelvic pain score of 0.8 may have resulted in a floor effect making it difficult to detect treatment differences. These data suggest that the daily pain scales used in the current study did not have the dynamic range necessary for this clinical trial and that patients with higher baseline pain scores would be a more appropriate population for future study. This could be achieved with revision of the daily pain scales and/or modification of entry criteria for pain. Notably, the pain scales used in this study were modified in subsequent studies.

In summary, the use of elagolix in this study demonstrated that elagolix has the potential to relieve endometriosis-associated pain for up to 24 weeks of treatment. Elagolix treatment significantly improved dysmenorrhea and dyspareunia during the first 12 weeks of treatment. Although nonmenstrual pelvic pain failed to show statistically significant results with these efficacy scales, a subsequent trial revealed a statistically significant improvement in both dysmenorrhea and nonmenstrual pelvic pain with elagolix 150 mg once daily using a modified daily pain scale with greater dynamic range and sensitivity.²⁷ Elagolix has the potential to become a new treatment strategy of partial estrogen suppression in women with endometriosis-related pain, with an acceptable safety profile. However, additional, more robust studies are warranted.

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Authors’ Note

Neurocrine Biosciences designed the study, and Neurocrine Biosciences, AbbVie, and the authors analyzed and interpreted the data. All authors contributed to the development of the content. The authors and AbbVie reviewed and approved the manuscript and maintained control over the final content.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this

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