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JEPPD
ISSN 2035-9969

Journal of Endometriosis and Pelvic Pain Disorders 2015; 7(2): 56-62
DOI: 10.5301/je.5000211

ORIGINAL ARTICLE

Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist: results from a phase 2, randomized controlled study

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ABSTRACT

Purpose: Elagolix is a novel, oral GnRH antagonist that dose-dependently suppresses estradiol levels. This study evaluated safety and efficacy of elagolix vs. leuprorelin acetate (LA) and placebo in women with endometriosis-associated pain.

Methods: In this multicenter, double-blind study, women with laparoscopically confirmed endometriosis were randomized to oral elagolix 150 or 250 mg once daily, placebo or 3.75 mg LA intramuscularly (i.m.) monthly for 12 weeks. Placebo and LA patients were re-randomized to elagolix, and elagolix patients continued treatment for another 12 weeks.

Results: Baseline demographics were similar among groups (mean age 31.7 years). Significantly greater reductions in monthly mean pelvic pain compared with placebo ($p<0.05$) were observed in both elagolix doses at week 4, elagolix 250 mg at week 8 and LA at weeks 4, 8 and 12. The mean (95% CI) percentage change in spinal bone mineral density (BMD) from baseline at week 12 was -1.05 (-1.68, -0.43), -0.80 (-1.53, -0.07) and -1.63 (-2.28, -0.99) for elagolix 150-mg, 250-mg and LA groups, respectively, compared with a mean percentage increase in placebo group (0.11 [-0.50, 0.71]). Headache was the most common adverse event for all treatment groups.

Conclusions: Both elagolix and LA reduced endometriosis-associated pain for up to 24 weeks of treatment and were associated with generally acceptable safety profiles in this study. Based on relatively small changes from baseline to week 12 in BMD, elagolix may offer a potential long-term treatment option for endometriosis-associated pain in affected women. Larger clinical studies with elagolix are warranted.

Trial Registration: Clinicaltrials.gov Identifier: NCT00797225.

Keywords: Elagolix, Endometriosis, GnRH antagonist, Leuprorelin acetate, Pelvic pain

Introduction

Endometriosis is a chronic, estrogen-dependent disease that often requires long-term therapy (1). Oral contraceptives and nonsteroidal antiinflammatory drugs (NSAIDs) are frequently used as first-line treatments for the management of endometriosis-associated pelvic pain, but many patients progress over time to second-line therapies, such as high-dose progestins or gonadotropin-releasing hormone (GnRH) agonists (2-5). Current guideline documents recommend using GnRH agonists with add-back therapy (6). Surgery may also be performed to alleviate endometriosis symptoms, but recurrence of pain is common (7, 8).

GnRH agonists are efficacious for the treatment of endometriosis-associated pain and exert their therapeutic effects through constant stimulatory input at the pituitary GnRH receptor (9, 10). Constant stimulation, in contrast to endogenous pulsatile stimulation, leads to down-regulation of GnRH receptors and complete suppression of the hypothalamic-pituitary-gonadal axis (9). However, this treatment completely suppresses ovarian estradiol concentrations and is associated with hypoestrogenic side effects, including unacceptable loss of bone mineral density (BMD) and vasomotor symptoms, which limit GnRH agonist treatment to 6 months without additional hormonal add-back therapy (11).

Elagolix is a novel, oral, short-acting GnRH antagonist, which has the ability to suppress the pituitary-ovarian axis in a dose-dependent manner – i.e., from partial suppression at

Accepted: March 23, 2015
Published online: May 23, 2015

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lower doses to full suppression at higher doses (12). Elagolix showed efficacy in suppressing endometriosis-associated pain at doses that partially suppress estrogen concentrations (13, 14).

This phase 2, randomized, double-blind study assessed the safety and efficacy of elagolix 150 mg and 250 mg and included placebo and an active comparator, leuprorelin acetate (LA).

Methods

Study design

Patients were randomized (on day 2-5 of menses) equally to receive oral elagolix 150 mg once daily (q.d.), elagolix 250 mg q.d., placebo or LA 1-month depot 3.75 mg intramuscularly (i.m.) for 12 weeks. Blinding was achieved using a double-ummy design. Thereafter, patients originally randomized to placebo or LA were re-randomized to one of the elagolix doses, and patients originally randomized to elagolix continued their dose assignment for an additional 12 weeks. Additional information on study design is provided in "Supplementary material", available online at www.j-endometriosis.com.

Patients

Eligible patients were women aged 18-45 years, with laparoscopically confirmed endometriosis within 60 weeks of screening, and a total Composite Pelvic Signs and Symptoms Score (CPSSS) ≥6 with a score of ≥2 for dysmenorrhea and a score of ≥1 for nonmenstrual pelvic pain. CPSSS is based on the Biberoglu-Behrman monthly recall scale addressing dysmenorrhea, dyspareunia, nonmenstrual pelvic pain (NMPP), pelvic tenderness and pelvic induration.

Patients were excluded if they were administered a GnRH agonist or 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, or if they had a history of unresponsiveness to GnRH agonist or antagonist treatment.

Patients were required to use 2 forms of nonhormonal contraception during screening, treatment and follow-up periods.

All patients provided informed consent, and the study protocol was approved by the country-specific ethics committee and was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996.

Efficacy measures

There was no prespecified primary efficacy end point for this phase 2 study. Efficacy measures included daily assessment of pelvic pain using an 11-point numerical rating scale (NRS) and daily assessment of dysmenorrhea and NMPP using a 4-point modified Biberoglu-Behrman scale (15) (0 = none, 1 = mild, 2 = moderate, 3 = severe) adapted for daily use. Assessments occurred at approximately the same time each day using an which was also used to record the daily use of analgesics for endometriosis-associated pain. Additional efficacy assessments included the dyspareunia component of the CPSSS, which was completed at baseline and at the end of weeks 4, 8, 12, 16, 20 and 24 and at the follow-up visit (or early termination). Quality of life (QoL) was assessed using the Endometriosis Health Profile-5 (EHP-5) core questionnaire, which assesses pain, control and powerlessness, emotional well-being, social support and self-image on a 5-point scale (0 = never, 25 = rarely, 50 = sometimes, 75 = often, 100 = always). The questionnaire was administered at baseline and at the end of weeks 4, 8, 12, 16, 20 and 24 and at the follow-up visit (or early termination).

Use of analgesics

Mild analgesics (e.g., naproxen, celecoxib, ibuprofen, mefenamic acid, paracetamol) and strong analgesics (e.g., hydrocodone, paracetamol and codeine, paracetamol and hydrocodone, ketorolac) were permitted on an "as needed" basis and were documented by the patients in their e-Diaries. Use of analgesics with a long half-life (e.g., controlled-release oxycodone) and prophylactic analgesic use was prohibited.

Safety monitoring

The incidence and severity of adverse events were recorded throughout the study. Blood samples for standard clinical laboratory tests and hormone levels were collected at baseline and the end of weeks 4, 8, 12, 16, 20 and 24 and at the follow-up visit (or early termination). Standard clinical laboratory tests were analyzed by a central laboratory (ICON Laboratories, Dublin, Ireland). Estradiol concentrations were determined by liquid chromatography with tandem mass spectrometry (LC/MS/MS) performed by a central laboratory (Celerion, Lincoln, NE, USA).

BMD of the spine and femur (total hip) 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 (BioClinica, Newtown, PA, USA). If BMD at the end of week 24 had decreased more than 3% from screening, an additional DXA scan at week 48 posttreatment was required. Start dates for the first and second posttreatment menses were collected at the posttreatment study visit.

Uterine bleeding and menstrual cycle assessment

The intensity of uterine bleeding, characterized as *none, light, moderate* or *heavy,* was collected daily through the e-Diary.

Statistical analysis

The planned sample size of 180 (45 patients per group) was expected to provide 0.80 power to detect a difference of 1.5 points between elagolix and placebo in change from baseline of the monthly mean NRS at week 12. The study was not powered to detect differences in safety parameters, including changes in BMD.

The safety analysis included all patients who received at least 1 dose of study drug. Intention-to-treat (ITT) analysis was used for efficacy analyses and included all randomized

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participants who received at least 1 dose of study drug and had at least 1 evaluable e-Diary report following randomization.

Monthly mean values (calculated for each participant as the mean of daily values between scheduled monthly visits) for all e-Diary assessments were summarized using descriptive statistics. The changes from baseline in monthly mean values of the NRS for overall endometriosis-associated pelvic pain, as well as dysmenorrhea, NMPP, dyspareunia (assessed monthly) and the percentage of days of analgesic use were analyzed using a mixed-effects repeated measures analysis of covariance model. The model included fixed effects for treatment, time, the treatment-by-time interaction, a random effect for participant, the baseline-by-time interaction and the baseline value as a covariate.

The percentage of days a participant reported any uterine bleeding was calculated as the total number of days a participant reported light, moderate or heavy bleeding divided by the total number of days the participant had a nonmissing e-Diary report of uterine bleeding within each specified interval. Descriptive statistics were calculated for the percentage of days participants had any uterine bleeding and for each bleeding intensity category.

Results

The study was conducted from 26 November 2008 to 24 February 2010 at 27 centers in Central Eastern Europe (Bulgaria, Hungary, Poland, Romania, Russia and Ukraine). A total of 174 patients were randomized (the patient flow chart is provided in "Supplementary material", available online at www.j-endometriosis.com). Patient demographics and baseline characteristics were similar between groups. The mean age of the population was 31.7 years, mean body mass index (BMI) was 22.6 kg/m^2, mean time since endometriosis diagnosis was 21.9 months and all patients were white. Thirteen patients prematurely discontinued the study during the treatment period: 3 (7%) in the placebo group, 5 (11.6%) in the elagolix 150-mg group, 3 (6.8%) in the elagolix 250-mg group and 2 (4.5%) in the LA group. The reasons for discontinuation included adverse events (2 patients in the elagolix 150-mg [hot flash and arthralgia] and 1 patient in the elagolix 250-mg group [rash]; Tab. I) noncompliance (3 patients in the elagolix 150-mg group), withdrawal of consent (1 patient each in the elagolix 150-mg and 250-mg groups), lack of efficacy (1 placebo patient), loss to follow-up (1 patient each in the placebo and elagolix 250-mg groups) and sponsor decision (1 patient each in the placebo and LA groups). Overall, 6 patients discontinued during the posttreatment phase (1 elagolix 150 mg, 2 elagolix 250 mg and 1 placebo/elagolix 150 mg, 1 placebo/elagolix 250 mg, and 1 LA/elagolix 150 mg).

Pelvic pain assessments

The monthly mean endometriosis-associated pelvic pain scores (average of daily scores) measured by NRS are shown in Figure 1A. Both elagolix doses at week 4 and elagolix 250-mg treatment at week 8 resulted in significantly greater reductions in pelvic pain from baseline compared with placebo ($p<0.05$). Treatment with LA resulted in significantly greater reductions in pelvic pain from baseline compared with placebo at weeks 4, 8 and 12 ($p<0.05$).

The monthly mean dysmenorrhea and NMPP scores are shown in Figure 1B and C, respectively. Elagolix and LA treatment significantly reduced monthly mean dysmenorrhea

TABLE I - Adverse events reported by ≥5% of patients

Event	Placebo, no. (%)	Elagolix 150 mg, no. (%)	Elagolix 250 mg, no. (%)	Leuprorelin acetate, no. (%)
Adverse events occurring during weeks 1-12				
Headache	2 (4.7%)	8 (18.6%)	4 (9.1%)	6 (13.6%)
Nausea	1 (2.3%)	3 (7.0%)	2 (4.5%)	0 (0.0%)
Vertigo	1 (2.3%)	3 (7.0%)	1 (2.3%)	0 (0.0%)
Adverse events occurring with elagolix treatment during weeks 1-24				
Headache	NA	10 (11.8%)	10 (11.5%)	NA
Nausea	NA	5 (5.9%)	5 (5.7%)	NA
Back pain	NA	1 (1.2%)	4 (4.6%)	NA
Bone density decreased	NA	4 (4.7%)	3 (3.4%)	NA
Vertigo	NA	5 (5.9%)	2 (2.3%)	NA
Treatment emergent adverse events leading to discontinuation				
Hot flash	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)
Rash	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)
Arthralgia	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)

NA = not applicable.

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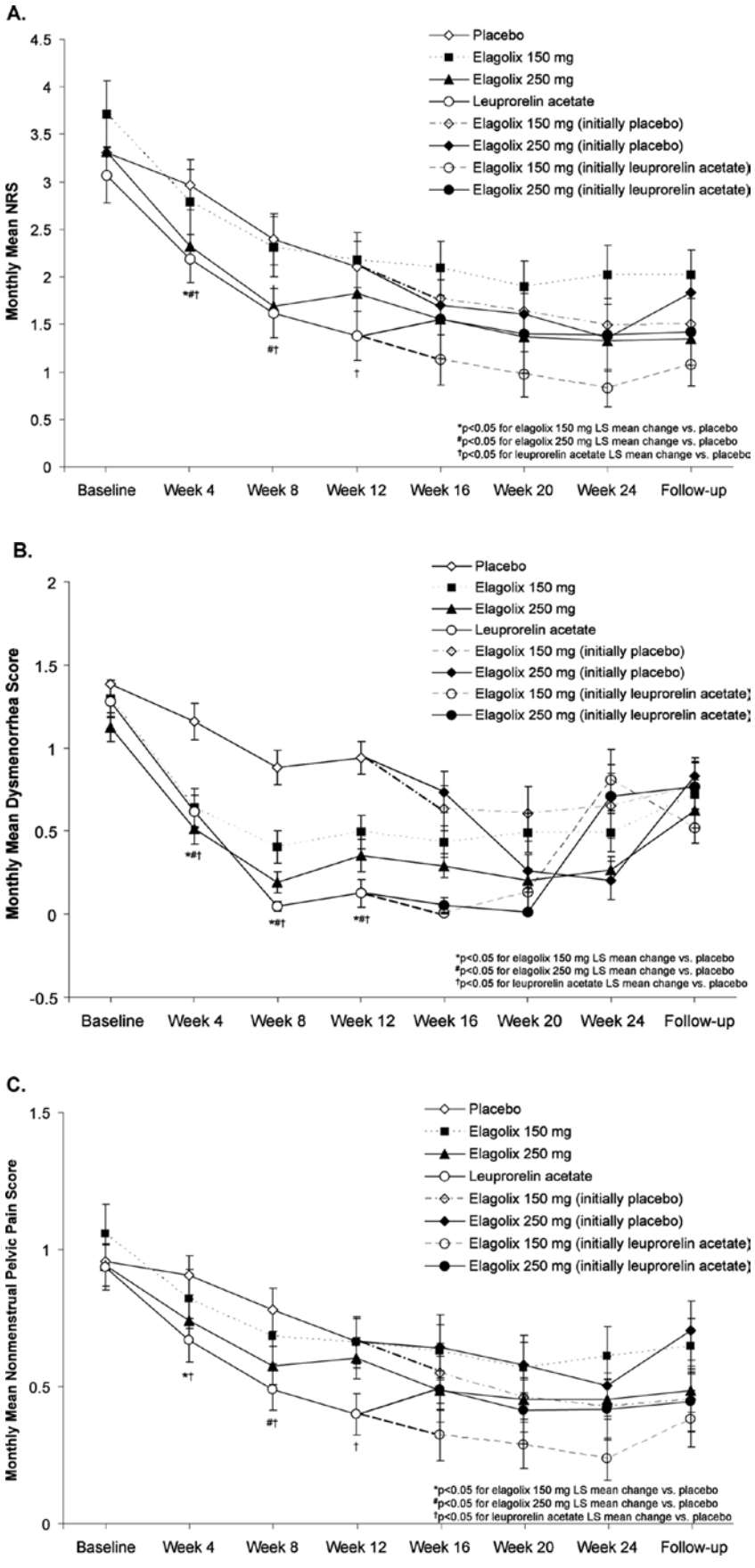

Fig. 1 - Monthly mean numerical rating scale (NRS) for endometriosis-associated pelvic pain **(A)**, dysmenorrhea (modified Biberoglu-Behrman scale) **(B)** and nonmenstrual pelvic pain (modified Biberoglu-Behrman scale) **(C)**. Whiskers are SEM.

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compared with placebo at weeks 4, 8 and 12 ($p<0.05$). It is notable that overall, baseline NMPP scores were low, with approximately 80% of the scores on nonmenstrual days being reported by patients as 0 to 1 (none or mild). Despite the low baseline, monthly mean NMPP was reduced from baseline in all 4 treatment groups; mean reductions were significantly greater ($p<0.05$) with elagolix 150 mg at week 4, elagolix 250 mg at week 8 and with LA at weeks 4, 8 and 12 compared with placebo. Leuprorelin showed greater reductions in NMPP changes from baseline than both dose groups of elagolix ($p<0.05$) at week 12.

Information regarding changes in dyspareunia is included in "Supplementary material."

Analgesic use

The baseline mean percentage of days with analgesic use were 14.2 ± 3.1, 15.1 ± 3.1, 11.7 ± 2.6 and 10.0 ± 2.1, for placebo, elagolix 150 mg, elagolix 250 mg and LA, respectively. The mean percentage of days with analgesic use was decreased from baseline in all treatment groups, with no significant differences between elagolix or LA treatment groups compared with placebo (at week 12, -6.2 ± 2.0, -4.4 ± 2.0, -8.3 ± 2.0 and -10.5 ± 2.0, for placebo, elagolix 150 mg, elagolix 250 mg and LA, respectively). During weeks 13-24, the mean percentage of days with analgesic use was similar to that observed during the first 12 weeks of treatment (week 24: -2.6 ± 2.2 and -4.0 ± 1.6 for placebo patients re-randomized to elagolix 150 mg and 250 mg, -8.0 ± 4.6 and -7.5 ± 2.1 for patients initially randomized to elagolix 150 and 250 mg, and -8.5 ± 3.4 and -10.9 ± 2.4 for LA patients re-randomized to elagolix 150 mg and 250 mg, respectively).

QoL results

There were improvements from baseline to week 12 in all 5 dimensions of the EHP-5 in all treatment groups. The magnitude of the reductions was similar in all groups for all dimensions except pain, for which the elagolix groups and the LA group had larger decreases compared with placebo (-19.0 ± 4.1, $p = 0.3453$; -25.0 ± 4.7, $p = 0.0392$; and -31.8 ± 3.9, $p<0.0001$, for elagolix 150 mg, elagolix 250 mg and LA, respectively, compared with -14.0 ± 4.8 for placebo). The differences between elagolix 150 mg, elagolix 250 mg vs. LA were statistically significant ($p = 0.006$ and $p = 0.0204$, respectively), which indicated a higher efficacy of LA in the pain dimension of EHP-5.

Safety

Both elagolix and LA were associated with acceptable safety profiles. Adverse events that occurred in ≥5% of patients are shown in Table I. Headache and nausea were the most frequently reported adverse events in the elagolix and LA groups compared with placebo. Serious adverse events were experienced by 3 patients who received elagolix; all were considered by the investigator to be unrelated to study drug (additional information provided in "Supplementary material").

There were 2 pregnancies during the study, both occurring in the treatment period. Both patients, 1 in the elagolix 250-mg group and 1 in the LA 3.75 mg/elagolix 150-mg treatment group, had healthy infants with no obstetrical complications.

Bone mineral density

The BMD measurements were collected at weeks 12 and 24 and are presented in Supplementary Tables II and III, available online as Supplementary material at www.j-endometriosis.com. The mean (95% CI) percentage change in spinal BMD from baseline at week 12 was -1.05 (-1.68, -0.43), -0.80 (-1.53, -0.07) and -1.63 (-2.28, -0.99) for the elagolix 150-mg, 250-mg and LA groups, respectively, compared with a mean percentage increase in the placebo group (0.11 [-0.50, 0.71]). At the femur, the mean (95% CI) percentage reduction in BMD from baseline at week 12 was -0.90 (-0.51, 0.33), -0.34 (-0.84, 0.16), -0.56 (-0.99, -0.14) and -1.12 (-1.63, -0.62) for placebo, elagolix 150-mg, 250-mg and LA groups, respectively. At week 24, mean (95% CI) percentage decreases were observed for both elagolix groups at the spine (-1.29 [-2.21, -0.37] and -1.86 [-2.72, -0.99] for 150 mg and 250 mg, respectively) and at the femur (-0.55 [-1.17, 0.07] and -0.70 [-1.22, -0.18] for 150 mg and 250 mg, respectively). For participants who received LA for 12 weeks and then re-randomized to elagolix 150 mg or 250 mg, at week 24, mean (95% CI) percentage decreases were observed for both elagolix groups at the spine (-2.90 [-4.29, -1.54] and -4.38 [-5.33, -3.42] for 150 mg and 250 mg, respectively) and at the femur (-1.78 [-2.57, -1.00] and -1.78 [-2.74, -0.83] for 150 mg and 250 mg, respectively). No statistical comparisons were conducted across treatment groups for BMD.

A total of 55 patients required repeat DXA scans at week 48 (additional information in "Supplementary material"), at which time BMD had generally increased slightly or remained similar to the week 24 measurement. None of these participants had abnormal Z-scores.

Estradiol levels

The summary of estradiol levels for the first 12 weeks for all treatment groups is presented in Supplementary Table IV. The summary of estradiol levels for the second 12 weeks as well as week 30 (6 weeks posttreatment) for all treatment groups is presented in the Supplementary Table V.

At baseline, all participants were within cycle day 2-5, and median estradiol concentrations were 39.1 pg/mL, 43.4 pg/mL, 47.5 pg/mL, 46.2 pg/mL for placebo, elagolix 150 mg, elagolix 250 mg and LA, respectively. During treatment weeks 4-12, median estradiol concentrations ranged from 49.5 to 87.9 pg/mL in the placebo group, 36.4 to 39.6 pg/mL in the elagolix 150-mg group, 22.0 to 26.2 pg/mL in the elagolix 250-mg group and were very low in the LA group, ranging from 3.6 to 6.4 pg/mL. During weeks 16 to 24, median estradiol concentrations for patients initially randomized to placebo were similar to those observed for the elagolix 150-mg and 250-mg groups during weeks 4-12. In patients originally randomized to LA, estradiol concentrations remained lower than those observed in the elagolix treatment groups until week 20 in the 150-mg group and week 24 in the 250-mg group.

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Uterine bleeding during treatment

The percentage of days with uterine bleeding (any, heavy, moderate and light) by study phase in the initial treatment randomization groups is summarized in Supplementary Table VI. The percentage of days with any uterine bleeding in placebo and LA participants re-randomized to elagolix is summarized in Supplementary Table VII. In the elagolix treatment groups, the percentage of days with any uterine bleeding decreased almost 50% during the treatment phase compared with screening. A similar result was observed in the LA group when comparing the mean percentage of days with any uterine bleeding during the screening phase with that in theentire treatment phase; however, consistent with the flare effect reported with LA, there was a small increase in the mean percentage of days with any uterine bleeding during the first 4 weeks of the treatment phase compared with screening. So, in contrast to LA that induces amenorrhea after the flare period, most participants treated with elagolix 150 mg q.d. and 250 mg q.d. still experienced light bleeding episodes, which was reflected by a 50% reduction in bleeding days during the entire treatment period.

Posttreatment menses

After discontinuation of study drug, the median number of days to the first posttreatment menses was 26.0 and 27.0 for placebo patients re-randomized to elagolix 150 mg and 250 mg, 22.5 and 26.0 for elagolix 150 mg and 250 mg patients, and 29.0 and 28.0 for LA patients re-randomized to elagolix 150 mg and 250 mg, respectively.

Discussion

At week 12, numerical decreases from baseline in NRS-measured endometriosis-associated pain were observed in all 4 treatment groups. The reductions were slightly larger with elagolix than with placebo, while the differences between LA and placebo were statistically significant at week 12. At week 4, all statistically significant improvement vs. placebo in endometriosis-associated pain was observed in all 3 treatment groups, whereas only the effects of elagolix 250 mg and LA were statistically significantly different from placebo. Both elagolix and LA treatment significantly reduced monthly mean dysmenorrhea scores at week 12 compared with placebo; however, changes in NMPP and dyspareunia in the elagolix treatment group did not reach statistical significance, while those in the LA group did. Again, consistent with its mechanism of action, causing full suppression of the pituitary-ovarian axis, LA showed greater reductions in NMPP than both doses of elagolix and also showed higher suppression in the pain dimension of EHP-5 than the elagolix dose groups.

The assessment of pain in endometriosis studies is challenging because the outcomes may be influenced by various factors, such as the type of pain scale used, the level of pain at baseline, variability in placebo effects in different patient populations, etc. Although the inclusion criteria required a total CPSSS ≥6 with a score of ≥2 for dysmenorrhea and a score of ≥1 for NMPP on a monthly recall scale, a substantial proportion of patients studied had relatively low baseline pain scores on the daily scales used to measure NRS, dysmenorrhea and NMPP. Thus, the potential to detect changes in endometriosis-associated pain, particularly NMPP, was limited because the daily scales did not seem to adequately reflect the experience of endometriosis pain by the patients in this study. A subsequent phase 2 study included women with moderate to severe pain and used modified daily pain scales in an effort to increase the ability (i.e., greater sensitivity) to detect changes (16). This was a randomized, placebo-controlled parallel group study, consisting of an 8-week double-blind period followed by a 16-week open-label period, in 137 patients with, with laparoscopically confirmed endometriosis and moderate to severe NMPP and dysmenorrhea, who were administered elagolix 150 mg daily or placebo. The primary outcomes of the study were the daily assessment of dysmenorrhea, NMPP and dyspareunia using a modified Biberoglu-Behrman scale. During the double-blind period, there were significantly greater mean reductions from baseline to week 8 in dysmenorrhea NMPP, and in the elagolix group compared with placebo (16). The results of this subsequent study incorporating these modifications and using a 150-mg daily dose of elagolix provide further support for the data from this present study.

The mean percentage of days with analgesic use was decreased from baseline in all treatment groups. However, analgesic use was relatively low at baseline in this study. In the current study, estradiol suppression was greater in patients who received LA compared with elagolix. Consistent with greater suppression of estradiol (17), there were greater reductions in BMD at the spine and femur in patients who received LA than in patients who received elagolix at week 12. A total of 55 patients required a repeat DXA scan at week 48, based on the protocol requirement if BMD at the end of week 24 had decreased more than 3% from screening. However, this threshold was close to the precision of DXA, which ranges from 0.969% to 2.101% and from 1.475% to 3.362% for spine and femoral neck, respectively (18).

Both elagolix and LA were associated with acceptable safety profiles in this study. Low rates of hot flashes were reported in all treatment groups, including the LA arm. This finding is in contrast to other studies with LA in women with endometriosis, which reported hot flash rates ranging from 11.1% to 84% (19, 20), depending on the study population and the method used to collect hot flash reports.

Despite the protocol requirement for the use of 2 forms of nonhormonal contraception, there were 2 pregnancies that occurred during the treatment period of this study, 1 in the elagolix treatment arm and the other in the LA/elagolix treatment arm. Both pregnancies resulted in healthy deliveries, without complications.

This study was conducted mostly in an Eastern European population, and the results may not be generalizable to the US or Western Europe population. For example, BMI scores in this study were generally low in comparison with those for American women. In addition, there was a marked placebo effect, which is not uncommon in the Eastern European population studied but may be smaller in the United States (21, 22). Reductions in BMD were also greater in this European population compared with a similar study in a US population (16). Furthermore, Eastern European women may have

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a different perception of vasomotor symptoms, including hot flashes, compared with women from the United States and Western Europe. These potential differences in study populations are speculative and warrant further investigation.

In summary, treatment with both elagolix and LA in this study was associated with an adequate safety profile and reduced endometriosis-associated pain for up to 24 weeks of treatment. However, larger clinical studies with elagolix are warranted. Elagolix may offer a new treatment option for endometriosis-associated pain in affected women.

Acknowledgement

The authors wish to acknowledge Colin Miller, PhD, of BioClinica (former Bio-Imaging) for his contributions to this study. Medical writing support was provided by Amanda J. Fein, PhD, an employee of AbbVie.

Disclosures

Financial support: This study was funded by Neurocrine Biosciences. Elagolix is being developed by AbbVie Inc. and Neurocrine Biosciences.
Conflicts of interest: N.A. was the coordinating investigator for the clinical trial reported herein. J.B., R.J. and C.O.B. are Neurocrine Biosciences employees and own Neurocrine Biosciences stock. K.C., E.G. and P.J. are AbbVie employees and own AbbVie stock.
Neurocrine Biosciences designed the study, 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; the authors maintained control over the final content.
Meeting presentation: Presented at the 94th annual meeting of the Endocrine Society, June 23-26, 2012, Houston, TX, USA.

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