

ORIGINAL ARTICLE

Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist

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ABSTRACT

BACKGROUND

Endometriosis is a chronic, estrogen-dependent condition that causes dysmenorrhea and pelvic pain. Elagolix, an oral, nonpeptide, gonadotropin-releasing hormone (GnRH) antagonist, produced partial to nearly full estrogen suppression in previous studies.

METHODS

We performed two similar, double-blind, randomized, 6-month phase 3 trials (Elaris Endometriosis I and II [EM-I and EM-II]) to evaluate the effects of two doses of elagolix — 150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group) — as compared with placebo in women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain. The two primary efficacy end points were the proportion of women who had a clinical response with respect to dysmenorrhea and the proportion who had a clinical response with respect to nonmenstrual pelvic pain at 3 months. Each of these end points was measured as a clinically meaningful reduction in the pain score and a decreased or stable use of rescue analgesic agents, as recorded in a daily electronic diary.

RESULTS

A total of 872 women underwent randomization in Elaris EM-I and 817 in Elaris EM-II; of these women, 653 (74.9%) and 632 (77.4%), respectively, completed the intervention. At 3 months, a significantly greater proportion of women who received each elagolix dose met the clinical response criteria for the two primary end points than did those who received placebo. In Elaris EM-I, the percentage of women who had a clinical response with respect to dysmenorrhea was 46.4% in the lower-dose elagolix group and 75.8% in the higher-dose elagolix group, as compared with 19.6% in the placebo group; in Elaris EM-II, the corresponding percentages were 43.4% and 72.4%, as compared with 22.7% ($P < 0.001$ for all comparisons). In Elaris EM-I, the percentage of women who had a clinical response with respect to nonmenstrual pelvic pain was 50.4% in the lower-dose elagolix group and 54.5% in the higher-dose elagolix group, as compared with 36.5% in the placebo group ($P < 0.001$ for all comparisons); in Elaris EM-II, the corresponding percentages were 49.8% and 57.8%, as compared with 36.5% ($P = 0.003$ and $P < 0.001$, respectively). The responses with respect to dysmenorrhea and nonmenstrual pelvic pain were sustained at 6 months. Women who received elagolix had higher rates of hot flashes (mostly mild or moderate), higher levels of serum lipids, and greater decreases from baseline in bone mineral density than did those who received placebo; there were no adverse endometrial findings.

CONCLUSIONS

Both higher and lower doses of elagolix were effective in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with endometriosis-associated pain. The two doses of elagolix were associated with hypoestrogenic adverse effects. (Funded by AbbVie; Elaris EM-I and EM-II ClinicalTrials.gov numbers, NCT01620528 and NCT01931670.)

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ENDOMETRIOSIS IS A CHRONIC, ESTROGEN-dependent, inflammatory condition that is characterized by the implantation of endometrial-like tissue outside the uterus and affects 6 to 10% of women of reproductive age.^{1,2} Endometriosis symptoms include dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia, as well as the less common symptoms of pain at ovulation, constipation, and painful urination.^{1,3} Endometriosis-associated pain can decrease the patient's quality of life and result in substantial economic burden.⁴⁻⁷ Dyspareunia can have profound interpersonal and psychological consequences.⁸

Endometriosis has multifactorial causes, including retrograde menstruation, genetic and environmental factors, alteration of the immune system, and ectopic differentiation of mesenchymal stem cells.^{9,10} Estrogen plays a necessary role in the pathophysiology of endometriosis,¹¹ since it promotes the implantation of endometrial tissue in the peritoneum, has proliferative and antiapoptotic effects in endometrial cells, and stimulates local and systemic inflammation.^{12,13} On the basis of the "estrogen threshold hypothesis," complete estrogen suppression may not be needed to control endometriosis-associated pain, and estrogen may be adjusted to a level that is adequate to control pain but minimizes hypoestrogenic effects.¹⁴

First-line therapies for endometriosis-related pain include nonsteroidal antiinflammatory drugs (NSAIDs) and progestin-containing oral contraceptives.³ Second-line therapies involve injectable depot formulations of gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate. Although the injectable agents are effective and reduce estrogen levels to postmenopausal levels, they are associated with side effects (e.g., progressive bone loss and severe vasomotor symptoms), which limit their use to 6 months without hormone-replacement therapy.^{3,15,16} Medical options remain limited. Progestins are associated with bleeding, weight gain, and mood changes,¹⁷ and endometriosis is often associated with progesterone resistance.¹⁸ Androgenic agents such as danazol are associated with acne, hirsutism, and changes in lipid profiles.¹⁹ Surgical ablation or excision of lesions can be effective; however, symptoms often recur within 12 months, and more radical surgery (hysterectomy or oophorectomy) is a last resort.^{1,20} Pain management usually requires repeated courses of medical therapies or multiple surgical treatments until menopause.^{3,21}

Elagolix is an oral, nonpeptide GnRH antagonist. Proof-of-concept phase 2 studies of elagolix showed efficacy in controlling both dysmenorrhea and nonmenstrual pelvic pain, with an acceptable safety profile at a dose (once-daily 150 mg) that produces partial estrogen suppression.²²⁻²⁴ A phase 1 study showed that elagolix (at a dose of 200 mg twice daily) led to nearly full estrogen suppression.²⁵

We performed two similar multicenter, double-blind, randomized, placebo-controlled, phase 3 trials (Elaris Endometriosis I and II [EM-I and EM-II]) of 6-month treatment with elagolix at two doses in women with moderate or severe endometriosis-associated pain.

METHODS

PATIENTS

Women underwent randomization for Elaris EM-I at 151 sites in the United States and Canada from July 2012 through May 2014 and for Elaris EM-II at 187 sites on five continents from November 2013 through July 2015. Premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain were eligible to participate. (A full list of inclusion and exclusion criteria is provided in the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Women were excluded if they had a z score of less than -1.5 for bone mineral density at the lumbar spine, femoral neck, or total hip at screening or clinically significant gynecologic conditions or chronic pain conditions unrelated to endometriosis.

TRIAL DESIGN AND OVERSIGHT

Each trial was divided into four intervals: a wash-out of hormonal therapies (if applicable); a screening period of up to 100 days, including two menstrual cycles, during which women switched from the use of usual analgesic agents to receive allowed rescue medication of an NSAID (500 mg of naproxen), an opioid according to country (e.g., 5 mg of hydrocodone plus 325 mg of acetaminophen), or both (Table S1 in the Supplementary Appendix); a 6-month treatment period; and a follow-up period of up to 12 months, unless the woman was enrolled in the corresponding 6-month extension study (Fig. S1 in the Supple-

mentary Appendix). Here, we report the results of the initial 6-month treatment period only.

Eligible women were randomly assigned by means of an interactive voice-response system in a 2:2:3 ratio to receive 150 mg of elagolix once daily (lower-dose group), 200 mg of elagolix twice daily (higher-dose group), or placebo. Women were instructed to use two forms of nonhormonal contraception; monthly pregnancy tests were performed. Trial visits were performed on day 1 and monthly through 6 months.

The trials were conducted in accordance with International Conference on Harmonisation guidelines and applicable regulations and ethical principles of the Declaration of Helsinki. All the women provided written informed consent. The sponsor, AbbVie, designed the trials and analyzed the data; the investigators and the sponsor jointly conducted the trials and gathered the data. All the authors had full access to the data and signed confidentiality agreements with the sponsor regarding the data. The first draft of the manuscript was written by a medical writer employed by the sponsor, with input from all the authors. All the authors reviewed and provided feedback on all subsequent versions of the manuscript and, along with the sponsor, made the decision to submit the manuscript for publication. All the authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol, available at NEJM.org.

EFFICACY END POINTS

The two primary efficacy end points were the proportion of women who had a clinical response with respect to dysmenorrhea and the proportion who had a clinical response with respect to nonmenstrual pelvic pain at 3 months. Each of these end points was measured as a clinically meaningful reduction in the pain score (on a scale ranging from 0 [no pain] to 3 [severe pain]) and a decreased or stable use of rescue analgesic agents (Table S2 in the Supplementary Appendix), as recorded in a daily electronic diary. The clinically meaningful threshold for the mean change from baseline, as compared with placebo, was -0.81 for dysmenorrhea and -0.36 for nonmenstrual pelvic pain in Elaris EM-I and -0.85 for dysmenorrhea and -0.43 for nonmenstrual pelvic pain in Elaris EM-II.

Key secondary efficacy end points were the mean changes from baseline to 3 months or

6 months, which were tested in a hierarchical order as follows: the score on the Numeric Rating Scale (0 [no pain] to 10 [worst pain ever]) at 3 months, dysmenorrhea at 6 months, nonmenstrual pelvic pain at 6 months, use of rescue analgesic agents (both NSAID and opioid pill counts) at 3 months and 6 months, dyspareunia (0 [none] to 3 [severe] or not applicable) at 3 months, and the use of a rescue opioid at 3 months. All the efficacy assessments and additional secondary end points (including the Patient Global Impression of Change and 30-item Endometriosis Health Profile questionnaires) are described in Table S3 in the Supplementary Appendix. Safety evaluations included endometrial assessments, measurement of bone mineral density, and laboratory measures (see the Methods section in the Supplementary Appendix).

STATISTICAL ANALYSIS

We calculated that the enrollment of 875 women in Elaris EM-I and 788 in Elaris EM-II (with the latter adjusted according to the withdrawal rate in Elaris EM-I) would provide a power of more than 90% to determine the two primary end points in each trial, assuming response rates of 55% in each elagolix group and 29% in the placebo group, at a two-sided alpha level of 0.025. Efficacy and safety analyses were performed in the modified intention-to-treat population, which included all the women who underwent randomization and received at least one dose of elagolix or placebo. Mean pain scores were calculated on the basis of levels at 35 days before day 1 (baseline) and levels during each month of treatment. We calculated the response thresholds for scores with respect to dysmenorrhea and nonmenstrual pelvic pain before unblinding, with a separate analysis of receiver operating characteristics that used answers of “much improved” and “very much improved” on the Patient Global Impression of Change questionnaire at 3 months to determine a clinically meaningful response. We calculated statistical significance, odds ratios (Table S4 in the Supplementary Appendix), and risk ratios (in post hoc analyses) on the basis of logistic-regression models comparing elagolix with placebo and using the categorization of “response” and “no response” as the dependent variable, trial group as the main effect, and the baseline score for dysmenorrhea or nonmenstrual pelvic pain as the covariates. We used the last-observation-carried-forward method for women who

prematurely discontinued the trial at or before 3 months. We performed a sensitivity analysis with imputation of no response for women who discontinued the trial before 3 months. We determined the statistical significance for differences between each elagolix dose and placebo for each key secondary end point from a separate mixed-effects model with repeated measures, using observed data with trial group as the main effect, the number of visits as the repeated measure, the baseline value as a covariate, and an interaction between trial group and visit. All reported P values are two-sided, and confidence intervals related to the two primary end points and sensitivity analyses are reported at the 97.5% level.

Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, versions 18.0 (Elaris EM-I) and 19.0 (Elaris EM-II). We used Fisher's exact test to compare the incidence of any adverse event (and of such events according to their preferred terms) in each elagolix group with the incidence in the placebo group. All reported P values are two-sided, and confidence intervals for safety end points are reported at the 95% level.

RESULTS

PATIENTS

A total of 872 women underwent randomization in Elaris EM-I and 817 in Elaris EM-II; of these women, 653 (74.9%) and 632 (77.4%), respectively, completed treatment. Details regarding enrollment, follow-up rates, and reasons for trial discontinuation are summarized in Figure S1 in the Supplementary Appendix. The trial groups had similar demographic and clinical characteristics at baseline (Table 1).

PRIMARY EFFICACY END POINTS

At 3 months, the proportion of women who met the clinical response criteria for each of the two primary end points was significantly greater among women who received each elagolix dose than among those who received placebo (Fig. 1). In Elaris EM-I, the percentage of women who had a clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents was 46.4% in the lower-dose group and 75.8% in the higher-dose group, as compared with 19.6% in the placebo group; in Elaris EM-II, the corresponding percentages

were 43.4% and 72.4%, as compared with 22.7% ($P<0.001$ for all comparisons). In Elaris EM-I, the percentage of women who had a clinically meaningful reduction in nonmenstrual pelvic pain and decreased or stable use of rescue analgesic agents was 50.4% in the lower-dose group and 54.5% in the higher-dose group, as compared with 36.5% in the placebo group ($P<0.001$ for all comparisons); in Elaris EM-II, the corresponding percentages were 49.8% and 57.8%, as compared with 36.5% ($P=0.003$ and $P<0.001$, respectively). The results of a sensitivity analysis with imputation of no response for women who discontinued the trial before 3 months were similar to those of the primary analysis (Table S5 in the Supplementary Appendix). The responses at 3 months with respect to dysmenorrhea and nonmenstrual pelvic pain were sustained at 6 months.

SECONDARY EFFICACY END POINTS

As compared with placebo, each elagolix dose resulted in a significant reduction from baseline to 3 months in endometriosis-associated pain, as measured with the Numeric Rating Scale, and significant reductions from baseline to 6 months in scores with respect to dysmenorrhea and nonmenstrual pelvic pain (Table 2). The reductions in dysmenorrhea and nonmenstrual pelvic pain were apparent at 1 month and were sustained at 6 months (Fig. S2 in the Supplementary Appendix). At 3 months and 6 months, women who received the higher dose of elagolix were taking a significantly lower amount of any rescue analgesic agent (as determined by the mean pill counts of NSAIDs, opioids, or both) than were those who received placebo; women in the lower-dose group did not have a significant reduction in the use of such agents. After the analysis of the rescue-analgesic end point, differences between the lower-dose elagolix group and the placebo group on the remaining hierarchically tested key secondary end points were not considered to be significant according to the protocol (Table 2). From baseline to 3 months, the mean reductions in the dyspareunia score and in the opioid pill count were significantly greater in the higher-dose elagolix group than in the placebo group (Table 2).

Significantly more women taking either dose of elagolix reported "much" or "very much" improvement on the Patient Global Impression of Change scale at 6 months than did those taking placebo (Fig. S3 in the Supplementary Appendix). Elagolix treatment resulted in a better quality of life than

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

Characteristic	Elaris EM-I		Elaris EM-II	
	Placebo (N = 374)	Elagolix, 150 mg Once Daily (N = 249)	Placebo (N = 360)	Elagolix, 150 mg Once Daily (N = 226)
Median age (range) — yr	31 (18–48)	32 (19–48)	33 (18–49)	34 (18–47)
Race — no. (%)†				
White	323 (86.4)	221 (88.8)	322 (89.4)	207 (90.4)
Black	33 (8.8)	19 (7.6)	29 (8.1)	18 (7.9)
Other	18 (4.8)	9 (3.6)	9 (2.5)	4 (1.7)
Body-mass index‡	28±6	28±6	27±6	27±7
No. of months since surgical diagnosis	45±30	41±29	46±39	42±36
Score for dysmenorrhea§	2.2±0.4	2.2±0.5	2.2±0.5	2.2±0.5
Score for nonmenstrual pelvic pain¶	1.6±0.5	1.6±0.5	1.6±0.5	1.7±0.5
Score for dyspareunia§	1.5±0.8	1.5±0.8	1.5±0.8	1.5±0.9
Score on Numeric Rating Scale¶¶	5.6±1.6	5.7±1.7	5.6±1.8	5.7±1.8
Mean lipid values				
LDL cholesterol — mg/dl	100.7	97.2	99.6	100.2
HDL cholesterol — mg/dl	55.7	55.6	59.1	59.9
Triglycerides — mg/dl	107.3	105.5	109.5	104.6
Ratio of LDL cholesterol to HDL cholesterol	1.93	1.87	1.80	1.78
Mean z score for bone mineral density				
Lumbar spine	0.5	0.5	0.5	0.3
Total hip	0.3	0.4	0.4	0.2
Femoral neck	0.2	0.4	0.4	0.3
Use of analgesic agents — no. (%)				
NSAID only	136 (36.4)	65 (26.1)	101 (28.1)	77 (34.1)
Opioid only	71 (19.0)	45 (18.1)	56 (15.6)	33 (14.6)
NSAID and opioid	140 (37.4)	105 (42.2)	169 (46.9)	95 (42.0)
None	27 (7.2)	34 (13.7)	34 (9.4)	21 (9.3)

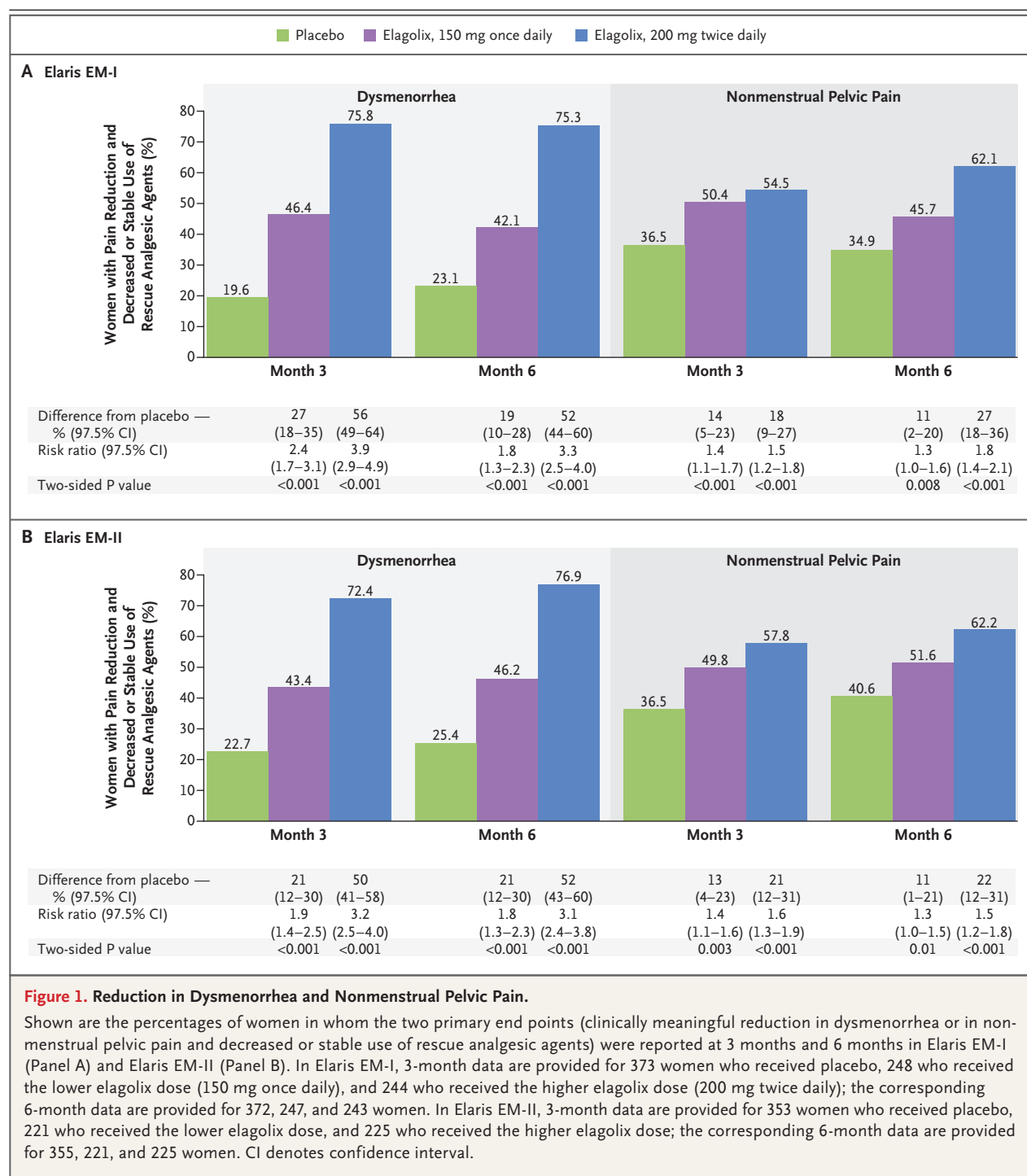
* Plus-minus values are means ±SD. There were no significant differences between the elagolix groups and the placebo group in either trial in tested categories except for the score for dysmenorrhea in the higher-dose group in Elaris EM-II ($P=0.03$). To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and NSAID nonsteroidal antiinflammatory drug.

† Race was reported by the women. "Other" includes Asian, multirace, American Indian or Alaskan Native, and Native Hawaiian or other Pacific Islander.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ 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.

¶¶ Women provided daily self-assessments of endometriosis-associated pain on a scale of 0 (no pain) to 10 (worst pain ever).



did placebo on the basis of the mean change from baseline to 3 months and 6 months on the 30-item Endometriosis Health Profile dimensions. These results differed significantly from those with placebo at 3 months and 6 months in

three of the six dimensions in Elaris EM-I and in four of the six dimensions in Elaris EM-II in the lower-dose group and in all six dimensions in the higher-dose group in both studies (Fig. S4 in the Supplementary Appendix).

Table 2. Key Secondary Efficacy End Points.*

Change from Baseline	Elaris EM-I			Elaris EM-II		
	Placebo	Elagolix, 150 mg Once Daily	Elagolix, 200 mg Twice Daily	Placebo	Elagolix, 150 mg Once Daily	Elagolix, 200 mg Twice Daily
Score on Numeric Rating Scale†						
At 3 mo						
No. of women	329	226	213	312	204	209
Change in score	-1.09±0.10	-1.74±0.12	-2.39±0.12	-1.33±0.10	-1.90±0.12	-2.55±0.12
Difference from placebo		-0.65±0.16‡	-1.30±0.16‡		-0.57±0.16‡	-1.22±0.16‡
Score for dysmenorrhea§						
At 6 mo						
No. of women	288	198	182	273	185	187
Change in score	-0.44±0.05	-0.89±0.06	-1.75±0.06	-0.52±0.05	-1.06±0.06	-1.65±0.06
Difference from placebo		-0.45±0.07‡	-1.32±0.08‡		-0.54±0.07‡	-1.13±0.07‡
Score for nonmenstrual pelvic pain§						
At 6 mo						
No. of women	288	198	182	273	185	187
Change in score	-0.31±0.04	-0.48±0.04	-0.72±0.04	-0.48±0.04	-0.63±0.04	-0.80±0.04
Difference from placebo		-0.16±0.06¶	-0.41±0.06‡		-0.15±0.06¶	-0.32±0.06‡
Use of rescue analgesic agent						
At 3 mo						
No. of women	329	226	213	312	204	209
Change in score	-0.29±0.03	-0.29±0.04	-0.55±0.04	-0.31±0.03	-0.36±0.04	-0.49±0.03
Difference from placebo		-0.01±0.05	-0.26±0.05‡		-0.05±0.04	-0.18±0.04‡
At 6 mo						
No. of women	288	198	182	273	185	187
Change in score	-0.27±0.04	-0.35±0.04	-0.56±0.05	-0.32±0.03	-0.40±0.04	-0.52±0.04
Difference from placebo		-0.07±0.06	-0.28±0.06‡		-0.08±0.05	-0.21±0.05‡
Score for dyspareunia§						
At 3 mo						
No. of women	246	171	153	226	145	150
Change in score	-0.29±0.04	-0.39±0.05	-0.49±0.05	-0.30±0.04	-0.39±0.05	-0.60±0.05
Difference from placebo		-0.09±0.07	-0.20±0.07¶		-0.09±0.07	-0.30±0.07‡
Use of rescue opioid						
At 3 mo						
No. of women	329	226	213	312	204	209
Change in score	-0.10±0.02	-0.07±0.03	-0.22±0.03	-0.12±0.02	-0.12±0.02	-0.21±0.02
Difference from placebo		0.03±0.04	-0.12±0.04¶		0.00±0.03	-0.08±0.03¶

* Plus-minus values are least-squares means ±SE. Outcomes are listed in the order of hierarchical statistical testing, which was stopped for the lower dose of elagolix (150 mg once daily) after the evaluation of rescue analgesic use at 3 months.

† Women provided daily self-assessments of endometriosis-associated pain on a scale of 0 (no pain) to 10 (worst pain ever).

‡ P<0.001.

§ Pain scores range from 0 (none) to 3 (severe) and were recorded in a daily electronic diary. Scores on the scale for dyspareunia were analyzed for women who recorded data other than “not applicable” at baseline and at one or more measurements after baseline.

¶ P<0.01.

|| The use of rescue NSAIDs or opioids was based on average pill counts.

SAFETY

More than 70% of women in each trial group reported at least one adverse event, with a significant difference in frequency between those receiving the higher dose of elagolix and those receiving placebo; 10% or less of the women discontinued their participation in the trial because of any adverse event (Table 3). The three most frequently reported adverse events in each trial were hot flushes, headache, and nausea; the incidence of hot flushes was significantly higher with each dose of elagolix than with placebo (Table 3, and Table S6 in the Supplementary Appendix). For the majority of women receiving elagolix who reported hot flushes, the maximum severity was mild or moderate; discontinuation due to hot flushes occurred in less than 1% of the women in the lower-dose group and in less than 3% of those in the higher-dose group (Table S7 in the Supplementary Appendix). The most frequently reported severe and serious adverse events are reported in Table S8 in the Supplementary Appendix. There was one death in Elaris EM-II, which was due to suicide by overdose with multiple nontrial medications in a woman who had been receiving the lower dose of elagolix for up to 31 days (Table 3).

At 6 months in the two trials, mean decreases from baseline in bone mineral density at the lumbar spine, femoral neck, and total hip were significantly greater in the elagolix groups than in the placebo group. The only exception was the between-group difference in bone mineral density at the femoral neck in Elaris EM-I, which was not significant in the lower-dose group (Fig. 2). In Elaris EM-I, at 6 months, the percentage of women with decreases of more than 5% in bone mineral density at the lumbar spine was 3.8% in the lower-dose elagolix group and 20.9% in the higher-dose elagolix group, as compared with 1.8% in the placebo group; in Elaris EM-II, the corresponding percentages were 2.3% and 16.4%, as compared with 1.1% (Fig. S5 in the Supplementary Appendix). In Elaris EM-I, the percentage of women with z scores for bone mineral density at the lumbar spine that were -1.5 or less after 6 months of treatment was 1.1% in the lower-dose elagolix group and 3.3% in the higher-dose group, as compared with 0.4% in the placebo group; in Elaris EM-II, the corresponding percentages were 0.6% and 4.9%, as compared with no women in the placebo group.

Elagolix treatment was associated with increas-

es from baseline to 6 months in lipid measurements, including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These increases were significantly higher in both elagolix groups than in the placebo group, except for HDL cholesterol in Elaris EM-I and triglycerides in both trials in the lower-dose elagolix groups (Table 3). There was a small but significant difference from placebo in the mean increases from baseline to 6 months in the ratio of LDL cholesterol to HDL cholesterol in the higher-dose group in each trial and in Elaris EM-I in the lower-dose group (Table 3). Less than 20% of the women in each elagolix group had levels of LDL cholesterol that were more than 160 mg per deciliter (4.14 mmol per liter)²⁶ or had levels of triglycerides of more than 200 mg per deciliter (2.26 mmol per liter)²⁶ at any time during treatment (Table 3). There were no significant differences between elagolix and placebo in the mean change from baseline to 6 months in the blood glucose level (Table S9 in the Supplementary Appendix).

There were numerical decreases from baseline to 6 months in endometrial thickness with elagolix treatment, although there were no statistical comparisons performed for endometrial measures; a higher proportion of women in each elagolix group had amenorrhea during months 1 through 6 than in the placebo group (Table S10 in the Supplementary Appendix). On the basis of endometrial-biopsy samples obtained in Elaris EM-I, at 6 months a greater proportion of women had normal quiescent or minimally stimulated endometrial patterns in the elagolix groups than in the placebo group; there were no pathological findings, including hyperplasia, in either elagolix group (Table S11 in the Supplementary Appendix).

There were 23 pregnancies during the intervention period in the two trials. Of the 8 pregnancies in the elagolix groups, there were 3 live births (with no congenital anomalies), 1 spontaneous abortion, 2 terminations of pregnancy, and 2 losses to follow-up (Table S12 in the Supplementary Appendix).

DISCUSSION

In two large, randomized, placebo-controlled trials, we found that women with moderate or severe endometriosis-associated pain who received two different doses of elagolix had significantly lower scores for dysmenorrhea and nonmenstrual

Table 3. Adverse Events and Changes in Serum Lipid Levels.*

Event	Elaris EM-I			Elaris EM-II		
	Placebo (N = 374)	Elagolix, 150 mg Once Daily (N = 249)	Elagolix, 200 mg Twice Daily (N = 248)	Placebo (N = 360)	Elagolix, 150 mg Once Daily (N = 226)	Elagolix, 200 mg Twice Daily (N = 229)
Adverse events — no. (%)†						
Any	277 (74.1)	201 (80.7)	205 (82.7)‡	260 (72.2)	179 (79.2)	194 (84.7)§
Any serious adverse event	12 (3.2)	2 (0.8)	7 (2.8)	12 (3.3)	12 (5.3)	5 (2.2)
Any severe adverse event	56 (15.0)	26 (10.4)	43 (17.3)	32 (8.9)	23 (10.2)	21 (9.2)
Any adverse event leading to discontinuation	22 (5.9)	16 (6.4)	23 (9.3)	22 (6.1)	10 (4.4)	23 (10.0)
Death	0	0	0	0	1 (0.4)¶	0
Adverse events with significant difference from placebo — no. (%) 						
Hot flush	26 (7.0)	59 (23.7)§	105 (42.3)§	37 (10.3)	51 (22.6)§	109 (47.6)§
Headache	37 (9.9)	38 (15.3)	43 (17.3)‡	51 (14.2)	42 (18.6)	52 (22.7)‡
Insomnia	9 (2.4)	16 (6.4)‡	18 (7.3)**	12 (3.3)	13 (5.8)	24 (10.5)§
Amenorrhea	1 (0.3)	8 (3.2)**	14 (5.6)§	1 (0.3)	11 (4.9)§	20 (8.7)§
Mood swings	10 (2.7)	10 (4.0)	11 (4.4)	8 (2.2)	13 (5.8)‡	6 (2.6)
Night sweats	5 (1.3)	6 (2.4)	14 (5.6)**	1 (0.3)	3 (1.3)	5 (2.2)‡
Arthralgia	8 (2.1)	9 (3.6)	8 (3.2)	11 (3.1)	7 (3.1)	16 (7.0)‡
Changes in serum lipid levels						
Total cholesterol						
No. of women	232	169	156	265	179	183
Percent change from baseline to 6 mo	-0.71±12.08	5.10±13.05§	13.46±13.86§	-0.56±11.80	4.55±11.78§	10.40±14.95§
LDL cholesterol						
No. of women	230	167	154	262	178	183
Percent change from baseline to 6 mo	-2.03±19.53	6.55±20.63§	17.08±21.55§	-0.70±19.53	5.73±19.00§	13.04±23.35§
Women with LDL cholesterol >160 mg/dl — no./total no. (%)††	13/354 (3.7)	21/235 (8.9)	28/228 (12.3)	18/341 (5.3)	22/215 (10.2)	35/215 (16.3)
HDL cholesterol						
No. of women	232	169	156	265	179	183
Percent change from baseline to 6 mo	4.04±17.20	5.07±15.86	8.19±16.08‡	1.44±15.77	4.48±14.76‡	7.72±17.52§
Triglycerides						
No. of women	232	169	156	265	179	183

Percent change from baseline to 6 mo	6.73±44.29	10.00±45.80	25.28±51.26§	3.82±40.53	7.74±40.52	18.08±48.61§
Women with triglycerides >200 mg/dl — no./total no. (%)††	53/355 (14.9)	42/235 (17.9)	39/228 (17.1)	43/341 (12.6)	28/215 (13.0)	40/215 (18.6)
Ratio of LDL cholesterol to HDL cholesterol						
No. of women	230	167	154	262	178	183
Percent change from baseline to 6 mo	-4.39±22.79	3.67±24.22§	10.02±22.86§	0.01±22.34	2.77±22.17	7.37±24.82§

* Plus-minus values are means ±SD. Adverse events were coded with the use of the *Medical Dictionary for Regulatory Activities*, versions 18.0 (Elaris EM-I) and 19.0 (Elaris EM-II).

† The severity of each adverse event was rated by the investigator as mild, moderate, or severe. Serious adverse events were defined as life-threatening, requiring hospitalization or medical or surgical intervention to prevent a serious outcome, or resulting in persistent disability or death.

‡ P<0.05.

§ P<0.001.

¶ The death in Elaris EM-II was due to suicide by overdose with multiple nontrial medications.

|| Listed are adverse events that occurred in at least 5% of the women in any elagolix group and for which the difference with placebo was significant. Events are listed in descending order of the overall incidence among women who received elagolix in Elaris EM-I.

** P<0.01.

†† Listed in this category are laboratory results that occurred at any time during the trial period.

pelvic pain than did those who received placebo after 3 months and 6 months of treatment. These results were supported by significantly better scores for endometriosis-associated pain on the Numeric Rating Scale at 3 months among those who received elagolix than among those who received placebo. In addition, women who received the higher dose of elagolix (200 mg twice daily) had significantly better results with respect to the use of rescue analgesic agents at 3 months and 6 months, dyspareunia at 3 months, and rescue opioid use at 3 months than did those receiving placebo. The observed improvements in quality of life were consistent with the primary and key secondary end points.

We determined the threshold for a pain-score reduction at 3 months with a receiver-operating-characteristics analysis using the responses on the Patient Global Impression of Change questionnaire, a procedure that is common in pain studies²⁷ but novel in this patient population. The magnitude of reduction in dysmenorrhea with elagolix appeared to be greater than the magnitude of reduction in nonmenstrual pelvic pain; dysmenorrhea is mostly dependent on cyclic changes in ovarian hormones, whereas the mechanism of nonmenstrual pelvic pain is more complex.²⁸

Oral elagolix had hypoestrogenic effects — including reduced bone mineral density, increased lipid levels, and an increased incidence of hot flashes — that were similar to those of injectable GnRH agonists, but the magnitude of the effects may differ. Both of the elagolix doses had an effect on bone mineral density, and the differences were significant as compared with placebo, although the difference between the lower dose of elagolix and placebo (range, -0.41% to -1.28% across measured regions) was smaller than that for the higher dose. Differences in the mean percent change in bone mineral density between the higher dose of elagolix and placebo ranged from -1.73% to -3.08% in measured regions, which is equivalent to absolute differences in the z score of approximately 0.15 to 0.30.²⁹ In ongoing analyses, we are assessing whether these decrements are reversible after the discontinuation of elagolix, as has been reported with leuprolide acetate.³⁰ After 6 months of treatment, fewer than 5% of the women in the elagolix groups had a z score of -1.5 or less for bone mineral density at the lumbar spine.

There was also a shift in the lipid profile with

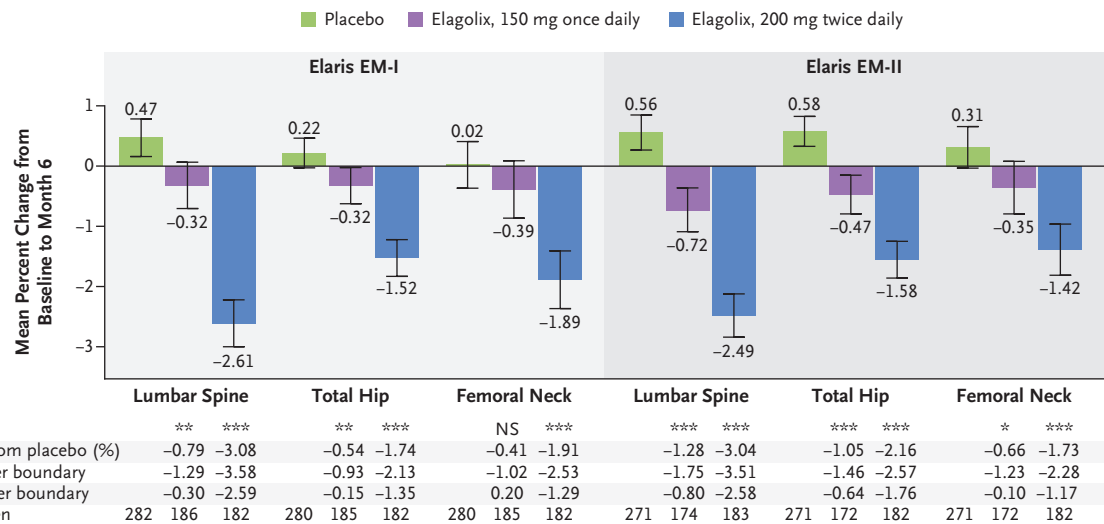


Figure 2. Mean Percent Change from Baseline to Month 6 in Bone Mineral Density.

At 6 months, all the percent differences in bone mineral density between the elagolix groups and the placebo group were significant, except for the between-group difference at the femoral neck in Elaris EM-I. One asterisk indicates $P < 0.05$, two asterisks $P < 0.01$, three asterisks $P < 0.001$, and NS not significant. The I bars indicate 95% confidence intervals.

elagolix treatment and included both favorable changes (increased HDL cholesterol level) and unfavorable changes (increased LDL cholesterol level). Some data suggest a potential increased risk of coronary heart disease in women with endometriosis,³¹ which may be partially associated with hysterectomy or oophorectomy. Although this young population was overall at low risk, it is unknown whether these changes in lipid levels would affect long-term cardiovascular risk. 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 per deciliter (0.38 mmol per liter) after 12 months of treatment.³²

We found no adverse effects on the endometrium after 6 months of elagolix treatment. In Elaris EM-I, the percentage of women who had normally quiescent or minimally stimulated tissue on endometrial-biopsy samples was greater in the elagolix groups than in the placebo group. This finding suggests that elagolix was associated with an antiproliferative effect at each dose and with endometrial atrophy at the higher dose, which was consistent with decreases in endometrial thickness at this dose.

Elagolix did not completely suppress ovulation at either of the two doses.²⁵ Although women were instructed to use dual nonhormonal contraception, pregnancies were reported during the

trials. There were no anomalous outcomes in the elagolix groups in these trials, but no conclusion on the effect of elagolix on pregnancy could be made, owing to the small number of pregnancies.

Although we did not perform prespecified statistical testing to compare the two elagolix doses, women in the higher-dose group had a greater reduction in pain and more severe hypoestrogenic adverse effects than those in the lower-dose group, which suggests the possibility of individual tailoring of these two doses to balance efficacy with hypoestrogenic effects. Observed reductions in pain and reports of hypoestrogenic adverse events were consistent with the mechanism of action of elagolix, which competitively inhibits GnRH receptors in the pituitary gland and leads to a rapid reduction in circulating gonadotropins and estradiol.²⁵ This mechanism is different from that of GnRH agonists, which after an initial stimulatory phase desensitize GnRH receptors in the pituitary and subsequently cause depletion of pituitary gonadotropins and full suppression of estradiol to levels that are equivalent to those associated with bilateral oophorectomy.³³ Agonists are effective in reducing both dysmenorrhea and nonmenstrual pelvic pain in women with endometriosis.³⁴ However, the profound estrogen suppression that is associated with their use leads to considerable hypoestrogenic effects. Such effects limit the

duration of treatment that can be administered without hormone-replacement therapy, and treatment cannot be dose-adjusted to alleviate these effects.^{1,3,32,35,36} For example, treatment with leuprolide acetate alone was associated with a mean percent decrease from baseline in bone mineral density at the lumbar spine of 3.2% at 6 months and 6.3% at 12 months; in addition, rates of treatment discontinuation were 6% because of hot flushes and 8% because of emotional changes.³²

The characteristics of our trial population of premenopausal women with endometriosis were similar to those of patients in epidemiologic studies of endometriosis and chronic pelvic pain.³⁷⁻³⁹ The safety and efficacy results of Elaris EM-II confirmed the results of Elaris EM-I, which showed the internal validity. The two trials were limited by the entry criteria and length of the intervention period. For example, the effect of elagolix was not examined in women with a z score of less than -1.5 for bone mineral density or in women with large endometriomas. Since surgical diagnoses had occurred within the previous 10 years, staging of endometriosis was incomplete and not used in the analysis. These trials were limited to 6 months of treatment; however, long-term or repeated courses of elagolix are likely to be needed for medical management. Data from the follow-up periods and 6-month extension studies may provide additional information about changes in bone mineral density and lipid levels over longer durations. We may also learn whether the changes associated with elagolix are persistent or whether they can be reversed with the discontinuation of treatment, findings that would further inform the risk-benefit profiles of each dose. Additional evaluation of the overall safety profile of multiple courses of treatment with elagolix is warranted.

In conclusion, the use of elagolix at two doses — 150 mg once daily and 200 mg twice daily — resulted in reductions in two of the hallmark pain symptoms of endometriosis, dysmenorrhea and nonmenstrual pelvic pain, after both 3 months and 6 months of treatment. Consistent with the mechanism of action, elagolix treatment resulted in hypoestrogenic effects, in-

cluding hot flushes and changes in bone mineral density and lipid levels.

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APPENDIX

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REFERENCES

- Giudice LC. Endometriosis. *N Engl J Med* 2010;362:2389-98.
- Missmer SA, Hankinson SE, Spiegelman D, et al. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol* 2004;104:965-74.
- Johnson NP, Hummelshoj L. Consensus on current management of endometriosis. *Hum Reprod* 2013;28:1552-68.
- Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril* 2011;96(2):366-373.e8.
- Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod* 2012;27:1292-9.
- Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. *Hum Reprod* 2016;31:712-22.
- Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril* 2006;86:1561-72.
- Vercellini P, Meana M, Hummelshoj L, Somigliana E, Viganò P, Fedele L. Priorities for endometriosis research: a proposed focus on deep dyspareunia. *Reprod Sci* 2011;18:114-8.
- Du H, Taylor HS. Contribution of bone marrow-derived stem cells to endometrium and endometriosis. *Stem Cells* 2007;25:2082-6.
- Bulun SE. Endometriosis. *N Engl J Med* 2009;360:268-79.
- Reis FM, Petraglia F, Taylor RN. Endometriosis: hormone regulation and clinical consequences of chemotaxis and apoptosis. *Hum Reprod Update* 2013;19:406-18.
- Brosens JJ, Gellersen B. The uterus under hormonal control — cycling for life. *Mol Cell Endocrinol* 2012;358:145.
- Bulun SE, Yang S, Fang Z, Gurates B, Tamura M, Sebastian S. Estrogen production and metabolism in endometriosis. *Ann N Y Acad Sci* 2002;955:75-85.
- Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. *Am J Obstet Gynecol* 1992;166:740-5.
- Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev* 2010;12:CD008475.
- Petta CA, Ferriani RA, Abrao MS, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod* 2005;20:1993-8.
- Dragoman MV, Gaffield ME. The safety of subcutaneously administered depot medroxyprogesterone acetate (104mg/0.65mL): A systematic review. *Contraception* 2016;94:202-15.
- Burney RO, Talbi S, Hamilton AE, et al. Gene expression analysis of endometrium reveals progesterone resistance and candidate susceptibility genes in women with endometriosis. *Endocrinology* 2007;148:3814-26.
- Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. *N Engl J Med* 2008;359:1136-42.
- Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update* 2009;15:441-61.
- Ofer A, Shulman LP, Singh SS. Improving the treatment and management of endometriosis: an overview of current and novel approaches. *Am J Obstet Gynecol* 2016;214:672.
- Carr B, Dmowski WP, O'Brien C, et al. Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. *Reprod Sci* 2014;21:1341-51.
- Diamond MP, Carr B, Dmowski WP, et al. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. *Reprod Sci* 2014;21:363-71.
- Carr B, Giudice L, Dmowski WP, et al. Elagolix, an oral GnRH antagonist for endometriosis-associated pain: a randomized, controlled study. *J Endometr Pelvic Pain Disord* 2013;5:105-15.
- Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab* 2017;102:1683-91.
- Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 — executive summary. *J Clin Lipidol* 2014;8:473-88.
- Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149-58.
- Stratton P, Berkley KJ. Chronic pelvic pain and endometriosis: translational evidence of the relationship and implications. *Hum Reprod Update* 2011;17:327-46.
- Watts NB, Leslie WD, Foldes AJ, Miller PD. 2013 International Society for Clinical Densitometry Position Development Conference: Task Force on Normative Databases. *J Clin Densitom* 2013;16:472-81.
- Surrey ES, Hornstein MD. Prolonged GnRH agonist and add-back therapy for symptomatic endometriosis: long-term follow-up. *Obstet Gynecol* 2002;99:709-19.
- Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and risk of coronary heart disease. *Circ Cardiovasc Qual Outcomes* 2016;9:257-64.
- Hornstein MD, Surrey ES, Weisberg GW, Casino LA. Leuprolide acetate depot and hormonal add-back in endometriosis: a 12-month study. *Obstet Gynecol* 1998;91:16-24.
- Maggi R, Cariboni AM, Marelli MM, et al. GnRH and GnRH receptors in the pathophysiology of the human female reproductive system. *Hum Reprod Update* 2016;22:358-81.
- Prentice A, Deary AJ, Goldbeck-Wood S, Farquhar C, Smith SK. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev* 2000;2:CD000346.
- Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. *Cochrane Database Syst Rev* 2003;4:CD001297.
- Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertil Steril* 2014;101:927-35.
- Gylfason JT, Kristjansson KA, Sverrisdottir G, Jonsdottir K, Rafnsson V, Geirsson RT. Pelvic endometriosis diagnosed in an entire nation over 20 years. *Am J Epidemiol* 2010;172:237-43.
- Leyland N, Casper R, Laberge P, Singh SS. Endometriosis: diagnosis and management. *J Obstet Gynaecol Can* 2010;32:Suppl 2:S1-S32.
- Parazzini F, Esposito G, Tozzi L, Noli S, Bianchi S. Epidemiology of endometriosis and its comorbidities. *Eur J Obstet Gynecol Reprod Biol* 2017;209:3-7.

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