1-23-2020

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ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

Uterine fibroids are hormone-responsive neoplasms that are associated with heavy menstrual bleeding. Elagolix, an oral gonadotropin-releasing hormone antagonist resulting in rapid, reversible suppression of ovarian sex hormones, may reduce fibroid-associated bleeding.

METHODS

We conducted two identical, double-blind, randomized, placebo-controlled, 6-month phase 3 trials (Elaris Uterine Fibroids 1 and 2 [UF-1 and UF-2]) to evaluate the efficacy and safety of elagolix at a dose of 300 mg twice daily with hormonal "add-back" therapy (to replace reduced levels of endogenous hormones; in this case, estradiol, 1 mg, and norethindrone acetate, 0.5 mg, once daily) in women with fibroid-associated bleeding. An elagolix-alone group was included to assess the impact of add-back therapy on the hypoestrogenic effects of elagolix. The primary end point was menstrual blood loss of less than 80 ml during the final month of treatment and at least a 50% reduction in menstrual blood loss from baseline to the final month; missing data were imputed with the use of multiple imputation.

RESULTS

A total of 412 women in UF-1 and 378 women in UF-2 underwent randomization, received elagolix or placebo, and were included in the analyses. Criteria for the primary end point were met in 68.5% of 206 women in UF-1 and in 76.5% of 189 women in UF-2 who received elagolix plus add-back therapy, as compared with 8.7% of 102 women and 10% of 94 women, respectively, who received placebo ($P<0.001$ for both trials). Among the women who received elagolix alone, the primary end point was met in 84.1% of 104 women in UF-1 and in 77% of 95 women in UF-2. Hot flushes (in both trials) and metrorrhagia (in UF-1) occurred significantly more commonly with elagolix plus add-back therapy than with placebo. Hypoestrogenic effects of elagolix, especially decreases in bone mineral density, were attenuated with add-back therapy.

CONCLUSIONS

Elagolix with add-back therapy was effective in reducing heavy menstrual bleeding in women with uterine fibroids. (Funded by AbbVie; Elaris UF-1 and Elaris UF-2 ClinicalTrials.gov numbers, NCT02654054 and NCT02691494.)

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N Engl J Med 2020;382:328-40.
DOI: 10.1056/NEJMoa1904351

Uterine fibroids (leiomyomas), common noncancerous neoplasms of the uterus, are symptomatic in up to 50% of affected women.[1-5] The primary symptom associated with uterine fibroids is heavy menstrual bleeding, which can lead to anemia.[6-8] Women with uterine fibroids can also have pelvic pain and pressure, urinary and gastrointestinal symptoms, infertility, and complications of pregnancy.[6,9-12] Uterine fibroids and their associated symptoms can have a major effect on a woman's quality of life, psychological and social well-being, and overall health,[13-18] and they impose a substantial economic burden on women and society.[16-18]

The primary management option for uterine fibroids is surgery, and hysterectomy is the most common intervention.[9,11] Alternatives to surgery include oral contraceptives, progestins, tranexamic acid, and a variety of interventional therapies (e.g., uterine-artery embolization and magnetic resonance–guided focused ultrasonography).[9,19-21] However, data from randomized, controlled trials showing the effectiveness of these treatment options in women with symptomatic fibroids are limited.[22] Injectable depot formulations of gonadotropin-releasing hormone (GnRH) agonists are also prescribed for heavy menstrual bleeding associated with uterine fibroids; however, such treatments induce long-lasting gonadal suppression resulting in adverse hypoestrogenic effects.[6,22,23] Data show that coadministration with progestins (e.g., leuprolide acetate with medroxyprogesterone acetate) may attenuate these effects.[24] An oral option that provides long-term, safe, and effective management of heavy menstrual bleeding in women with uterine fibroids would be a useful alternative to existing therapies.

Elagolix is an oral, nonpeptide GnRH antagonist that results in rapid, reversible suppression of gonadotropins and ovarian sex hormones in women.[25-27] These effects occur within 24 hours after the initiation of treatment and can be readily reversed on discontinuation of the drug, owing to its short half-life.[25] Elagolix is approved for the management of moderate-to-severe endometriosis-associated pain; when administered alone, it is associated with hypoestrogenic effects such as decreased bone mineral density and vasomotor symptoms that are consistent with its mechanism of action.[27] In a phase 2b study involving women with uterine fibroids, elagolix at a total daily dose of 600 mg with and without hormonal "add-back" therapy (to replace reduced levels of endogenous hormones) was effective in reducing menstrual bleeding and had a favorable safety profile. Add-back therapy attenuated decreases in bone mineral density and other hypoestrogenic effects, as observed in other studies.[28,29]

We report the results of two identical, double-blind, randomized, placebo-controlled, 6-month phase 3 trials, Elaris Uterine Fibroids 1 and 2 (UF-1 and UF-2). The objective of both trials was to assess the efficacy and safety of elagolix with add-back therapy, as compared with placebo, in the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. We also assessed hypoestrogenic effects in women who received elagolix with add-back therapy, as compared with elagolix alone.

METHODS

TRIAL DESIGN AND OVERSIGHT

UF-1 was conducted at 76 sites in the United States (including Puerto Rico) from December 2015 through December 2018, and UF-2 was conducted at 77 sites in the United States and Canada from February 2016 through January 2019. UF-1 and UF-2 were registered separately, and therefore the results are reported individually in this article. One patient in UF-1 and three patients in UF-2 who underwent randomization were enrolled before the trial registration date on ClinicalTrials.gov because of administrative error.

Each trial consisted of a period of washout of hormonal medication (if applicable) (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), a screening period of 2.5 to 3.5 months, a 6-month treatment period, and a 12-month follow-up period (or a corresponding extension study) (Fig. S1). Results of the 6-month treatment period are reported here.

Women were randomly assigned within 10 days after the start of their menses by means of an interactive response technology system in a 2:1:1 ratio to receive elagolix at a dose of 300 mg twice daily with add-back therapy (estradiol, 1 mg, and norethindrone acetate, 0.5 mg, once daily), elagolix at a dose of 300 mg twice daily alone, or placebo in a matched, double-blind, double-dummy manner. Women who received elagolix alone were included as a reference group to characterize the effects of add-back therapy.

The trials were conducted in accordance with the guidelines of the International Council for Harmonisation and applicable regulations and ethical principles of the Declaration of Helsinki. The study protocols were approved by the Schulman Institutional Review Board for central sites and by an institutional review board, ethics committee, or both for all other trial sites. All the women provided written informed consent. The trial sponsor, AbbVie, designed the trials and held and analyzed the data; the investigators and the sponsor jointly conducted the trials and gathered and interpreted the data. All the authors had full access to the data, signed confidentiality agreements with the sponsor regarding the data, and 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. The first draft of the manuscript was written by medical writers employed by the sponsor, with input from all the authors. All the authors critically 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.

PATIENTS

Eligible participants were premenopausal women who were between the ages of 18 and 51 years at the time of screening and who had an ultrasonography-confirmed diagnosis of uterine fibroids and heavy menstrual bleeding, as defined by more than 80 ml of menstrual blood loss per menstrual cycle for at least two separate cycles. Menstrual blood loss was measured by the alkaline hematin method, which objectively quantified the amount of blood in sanitary products collected (Supplemental Methods section 1D in the Supplementary Appendix).[30] Women were excluded if they were pregnant or if they had a persistent or complex ovarian cyst, cancer, pelvic inflammatory disease, a history of osteoporosis, or a bone mineral density T score of –1.5 or less at the lumbar spine, total hip, or femoral neck.

ASSESSMENTS AND END POINTS

All bleeding end points were assessed by means of the alkaline hematin method during the screening and treatment periods. If a woman did not return any used sanitary products at any visit during the treatment period, she was asked a standardized question to determine whether she had had any bleeding or spotting since her last trial visit. If no bleeding was reported over an interval, the menstrual blood loss over the interval was counted as zero. Safety evaluations included the assessment of adverse events, bone mineral density, lipid and liver profiles, endometrial thickness and biopsy results, ovarian cysts, and pregnancy (Supplemental Methods section 1E).

The primary end point was menstrual blood loss of less than 80 ml during the final month and at least a 50% reduction in menstrual blood loss from baseline to the final month. Women who met these two criteria but who had prematurely discontinued elagolix or placebo owing to adverse events or lack of efficacy or who had undergone surgery or invasive intervention for uterine fibroids during the trial were categorized as not having met the criteria for the primary end point.

Ranked secondary end points in hierarchical order were the following: the change from baseline in menstrual blood loss at the final month; the percentage of women who had suppression of bleeding (not accounting for spotting) at the final month; the change from baseline in menstrual blood loss at 6 months; the change from baseline in menstrual blood loss at 3 months; the percentage of women with a baseline hemoglobin level of 10.5 g per deciliter or less who had an increase in the hemoglobin level of more than 2 g per deciliter at 6 months; and the change from baseline in menstrual blood loss at 1 month. Other prespecified efficacy end points are listed in Table S2. Women were also asked to report their symptoms over the previous 4 weeks on the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire. This questionnaire includes a symptom severity score (scores range from 0 to 100, with higher scores indicating increased severity) and a health-related quality-of-life total score that is the sum of scores on six subscales (concern, activities, energy and mood, control, self-consciousness, and sexual function). Scores on the health-related quality-of-life portion of the questionnaire range from 0 to 100, with higher scores indicating a better quality of life.[31]

STATISTICAL ANALYSIS

For each trial, we calculated that a sample of approximately 400 women would provide at least 90% power with a 0.05 two-sided significance

level to detect a difference between the group of women who received elagolix with add-back therapy and the placebo group in the primary end point, assuming response rates of 60% among the women who received elagolix with add-back therapy and 30% in the placebo group, based on results from a previous phase 2b study of elagolix.[32] Efficacy and safety analyses were performed in all the women who underwent randomization and received at least one dose of elagolix or placebo, including those who prematurely discontinued elagolix or placebo or withdrew consent. We performed primary efficacy comparisons between the group of women who received elagolix with add-back therapy and the placebo group; we did not perform efficacy comparisons between the group of women who received elagolix with add-back therapy and those who received elagolix alone. Comparisons between the two elagolix groups were limited to evaluating changes in bone mineral density.

All statistical tests were performed with the use of SAS software (version 9.4), with a 0.05 two-sided significance level and 95% confidence interval. The baseline value for menstrual blood loss was defined as the mean of the total menstrual blood loss from all used sanitary products returned during all qualified menstrual cycles before or on trial day 1. Baseline for all other variables was defined as the last nonmissing measurement obtained before or on trial day 1, unless otherwise specified. For all women who underwent randomization and received treatment, the final month was defined as the last 28 days before and including the last treatment period visit date (if data on menstrual blood loss [measured with the use of the alkaline hematin method] that could be evaluated were available between the last treatment period visit date and the last dose date, then the last dose date was used). Missing data on menstrual blood loss in the final month were imputed with the use of multiple imputation (Supplemental Methods section 1F).

The primary end point was analyzed with the use of a logistic-regression model with treatment as the main effect and baseline menstrual blood loss as a covariate. For ranked secondary end points, the change in menstrual blood loss from baseline to the final month was based on data from multiple imputation for the primary efficacy analysis and analyzed with the use of a one-way analysis of covariance model with treatment as the main effect and baseline menstrual blood loss as a covariate. Changes in observed menstrual blood loss from baseline to 1, 3, and 6 months were analyzed with the use of a mixed model for repeated measures, with the fixed categorical effects of treatment, month, and treatment-by-month interaction and the continuous fixed covariate of baseline menstrual blood loss. The percentage of women who had suppression of bleeding at the final month and the percentage of women with a baseline hemoglobin level of 10.5 g per deciliter or less who had an increase in the hemoglobin level of more than 2 g per deciliter at 6 months were each analyzed with the use of a Pearson's chi-square test or Fisher's exact test (if ≥20% of the cells in the categorical table had expected counts of <5). The change from baseline to 6 months in the variables of the UFS-QOL questionnaire was analyzed with the use of an analysis of covariance model, with treatment as the main effect and baseline value as a covariate. Other results, including results of the sensitivity analyses for the primary end point and safety analyses, are provided in Supplemental Methods sections 1F and 1G.

RESULTS

PATIENTS

A total of 413 women in UF-1 and 378 in UF-2 underwent randomization; all but 1 woman in UF-1 received elagolix or placebo and were included in the efficacy and safety analyses. Of the women who underwent randomization and received elagolix or placebo, 328 in UF-1 (79.6%) and 289 in UF-2 (76.5%) completed the 6-month treatment period. Similar percentages of women prematurely discontinued treatment across all trial groups (Fig. S1). Table 1 summarizes the baseline characteristics of the patients.

PRIMARY EFFICACY END POINT

In the primary efficacy analysis with multiple imputation for missing data, significantly greater percentages of women who received elagolix with add-back therapy (68.5% of 206 women in UF-1 and 76.5% of 189 women in UF-2) met the criteria for the primary end point, as compared with women who received placebo (8.7% of 102 women in UF-1 and 10% of 94 women in UF-2)

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

Characteristic	Elaris UF-1			Elaris UF-2		
	Placebo (N=102)	Elagolix Alone (N=104)	Elagolix with Add-Back Therapy (N=206)	Placebo (N=94)	Elagolix Alone (N=95)	Elagolix with Add-Back Therapy (N=189)
Age — yr	41.6±5.7	42.6±5.2	42.6±5.3	42.5±5.4	42.2±5.4	42.5±5.3
Race — no./total no. (%)†						
Black	70/102 (68.6)	69/103 (67.0)	141/206 (68.4)	63/94 (67)	66/95 (69)	124/188 (66.0)
White	30/102 (29.4)	27/103 (26.2)	59/206 (28.6)	30/94 (32)	27/95 (28)	59/188 (31.4)
Other	2/102 (2.0)	7/103 (6.8)	6/206 (3.0)	1/94 (1)	2/95 (2)	5/188 (2.7)
Missing data	0	1	0	0	0	1
Body-mass index‡	33.8±7.7	33.4±7.7	33.3±6.8§	33.8±7.2	34.5±7.9	33.2±6.9
Menstrual blood loss/menstrual cycle — ml	255.3±174.0	248.9±169.6	238.0±150.1	254.3±178.5	224.9±146.2	228.5±148.8
Hemoglobin level — g/dl	11.0±1.4	10.6±1.5	11.1±1.5	11.0±1.6	11.0±1.6	11.1±1.5
Uterine volume — cm^3						
Measured with TAU or TVU	478.1±356.9	499.6±437.9	474.9±388.2	549.6± 452.1	537.3±521.9	496.1±381.6
Measured with MRI¶	561.9±437.2	617.0±582.3	508.6±342.2	798.6±730.9	675.7±906.2	676.8±559.1
Average fibroid volume — cm^3						
Measured with TAU or TVU‖	52.1±72.2	44.2±64.2	52.0±69.7	73.3±100.4	67.4±132.3	57.3±104.8
Measured with MRI**	73.1±98.1	60.2±70.3	66.0±73.7	104.3±120.5	83.3±130.8	72.0±68.2
UFS-QOL score††						
Symptom severity score‡‡	61.7±19.2	60.4±22.5	57.3±22.2	60.5±23.4	63.7±20.4	60.9±21.6
Health-related quality-of-life total score§§	40.7±20.3	42.5±23.3	44.1±23.5	43.0±22.8	42.2±24.0	43.3±24.2
Bone mineral density z score						
Lumbar spine	0.9±1.0	1.1±1.2	1.0±1.0§	1.1±1.1	0.9±1.2	1.1±1.2
Total hip	0.7±0.9	0.8±0.9	0.8±0.9§	0.7±1.0	0.8±1.0	0.8±0.9
Femoral neck	0.5±0.8	0.6±0.9	0.6±0.9§	0.6±0.9	0.6±0.9	0.6±0.9

* Plus–minus values are means ±SD. MRI denotes magnetic resonance imaging, TAU transabdominal ultrasonography, and TVU transvaginal ultrasonography.

† Race was reported by the women.

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

§ Data shown are for 205 patients.

¶ For the Elaris UF-1 trial, data shown are for 48 patients who received placebo, 51 patients who received elagolix alone, and 96 patients who received elagolix with add-back therapy. For the Elaris UF-2 trial, data shown are for 51 patients who received placebo, 52 patients who received elagolix alone, and 89 patients who received elagolix with add-back therapy.

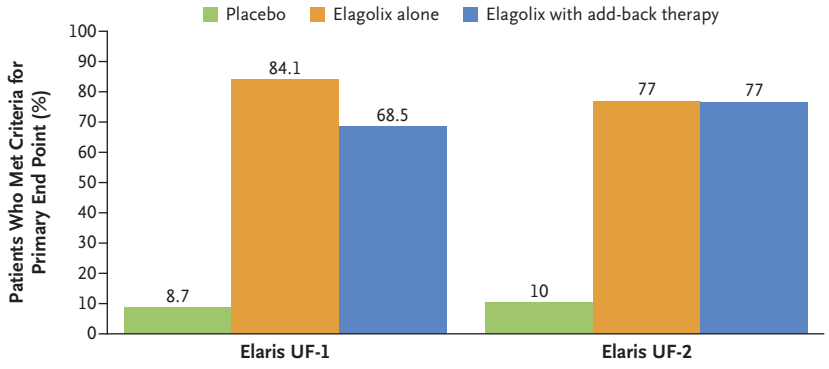
‖ For the Elaris UF-1 trial, data shown are for 100 patients who received placebo, 102 patients who received elagolix alone, and 203 patients who received elagolix with add-back therapy. For the Elaris UF-2 trial, data shown are for 92 patients who received placebo, 95 patients who received elagolix alone, and 186 patients who received elagolix with add-back therapy.

** For the Elaris UF-1 trial, data shown are for 47 patients who received placebo, 45 patients who received elagolix alone, and 83 patients who received elagolix with add-back therapy. For the Elaris UF-2 trial, data shown are for 45 patients who received placebo, 52 patients who received elagolix alone, and 92 patients who received elagolix with add-back therapy.

†† On the Uterine Fibroid Symptom and Quality of Life (UFS-QOL) questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. Total scores for health-related quality of life range from 0 to 100, with higher scores indicating a better quality of life.

‡‡ For the Elaris UF-1 trial, data shown are for 102 patients who received placebo, 103 patients who received elagolix alone, and 206 patients who received elagolix with add-back therapy. For the Elaris UF-2 trial, data shown are for 92 patients who received placebo, 94 patients who received elagolix alone, and 186 patients who received elagolix with add-back therapy.

§§ For the Elaris UF-1 trial, data shown are for 102 patients who received placebo, 103 patients who received elagolix alone, and 206 patients who received elagolix with add-back therapy. For the Elaris UF-2 trial, data shown are for 90 patients who received placebo, 94 patients who received elagolix alone, and 185 patients who received elagolix with add-back therapy.



Difference from placebo — %		75.4	59.8		66.4	66.0
(95% CI)		(66.2–84.6)	(51.1–68.5)		(55.5–77.3)	(57.1–75.0)
Risk ratio		9.7	7.9		7.1	7.2
(95% CI)		(5.0–18.9)	(4.1–15.5)		(3.8–13.4)	(3.9–13.5)
Two-sided P value			<0.001			<0.001
No. of women	102	104	206	94	95	189
No. imputed by multiple imputation	8	3	16	6	11	12

Figure 1. Reduction in Heavy Menstrual Bleeding in Women with Uterine Fibroids.

Shown are the percentages of women who met the criteria for the primary end point (a menstrual blood loss [MBL] volume of <80 ml in the final month and a ≥50% reduction in MBL volume from baseline to the final month) in the two trials. A significantly greater percentage of women who received elagolix with add-back therapy met the criteria for the primary end point than women who received placebo. The final month was defined as the last 28 days before and including the last treatment period visit date (if data on menstrual blood loss [measured with the use of the alkaline hematin method] that could be evaluated were available between the last treatment period visit date and the last dose date, then the last dose date was used). CI denotes confidence interval.

(P<0.001 for the two trials) (Fig. 1). Among women who received elagolix alone, 84.1% of 104 women in UF-1 and 77% of 95 women in UF-2 met the criteria for the primary end point. Results of all sensitivity analyses of the primary end point were similar to those of the primary analysis (Table S3).

RANKED SECONDARY AND OTHER EFFICACY END POINTS

Elagolix with add-back therapy, as compared with placebo, resulted in significant improvements in the prespecified ranked secondary outcomes: a greater reduction in menstrual blood loss from baseline to the final month, a higher percentage of women with suppression of bleeding at the final month, a greater reduction in menstrual blood loss from baseline to 6 months and 3 months, a higher percentage of women with a baseline hemoglobin level of 10.5 g per deciliter or less who had an increase in the hemoglobin level of more than 2 g per deciliter at 6 months, and a greater reduction in menstrual blood loss from baseline to 1 month (Table 2). (Reductions in menstrual blood loss over time are shown in Figure S2.) In the group of women who received elagolix with add-back therapy, 48.1% in UF-1 and 52.9% in UF-2 had amenorrhea (no bleeding or spotting) in the final month (as compared with 4% and 5%, respectively, in the placebo group); the same percentages of women also had control of bleeding (≤1 day of spotting) in the final month (Table S4). (Results of measures of hemoglobin, uterine volume, and average fibroid volume are shown in Figures S3 through S5.)

On the UFS-QOL questionnaire, scores for symptom severity range from 0 to 100, with higher scores indicating increased severity. The least-squares mean (±SE) change in symptom severity from baseline to 6 months in women who received elagolix with add-back therapy was −33.2±1.61 in UF-1 and −41.4±1.60 in UF-2 (as compared with −10.3±2.25 and −7.9±2.28, respectively, in women who received placebo). On the health-related quality of life total score portion of the questionnaire, scores range from 0 to 100, with higher scores indicating a better quality of

Table 2. Key Secondary Efficacy End Points.*

End Point	Elaris UF-1			Elaris UF-2		
	Placebo (N=102)	Elagolix Alone (N=104)	Elagolix with Add-Back Therapy (N=206)	Placebo (N=94)	Elagolix Alone (N=95)	Elagolix with Add-Back Therapy (N=189)
Volume of menstrual blood loss at final mo — ml†						
No. of women with data	102	104	206	94	95	189
Change from baseline — least-squares mean (95% CI)	0.8 (−28.3 to 30.0)	−221.5 (−249.9 to −193.1)	−176.7 (−197.1 to −156.3)	−4.3 (−34.5 to 26.0)	−198.8 (−229.0 to −168.5)	−168.8 (−189.8 to −147.8)
Difference from placebo (95% CI)		−222.3 (−263.0 to −181.6)	−177.5 (−213.3 to −141.7)		−194.5 (−237.1 to −152.0)	−164.6 (−201.5 to −127.6)
P value‡			<0.001			<0.001
Suppression of bleeding during final mo†§						
Women with suppression — no./total no. (%)	4/91 (4)	79/94 (84)	104/183 (56.8)	4/85 (5)	72/81 (89)	105/172 (61.0)
Difference from placebo (95% CI)		79.6 (71.13 to 88.16)	52.4 (44.11 to 60.76)		84.2 (75.99 to 92.37)	56.3 (47.77 to 64.91)
P value¶			<0.001			<0.001
Volume of menstrual blood loss at 6 mo — ml						
No. of women with data	71	67	132	64	53	124
Change from baseline — least-squares mean (95% CI)	−2.3 (−28.9 to 24.4)	−236.2 (−263.3 to −209.2)	−194.7 (−214.0 to −175.5)	28.5 (−4.3 to 61.4)	−223.7 (−259.1 to −188.3)	−198.1 (−221.5 to −174.7)
Difference from placebo (95% CI)		−234.0 (−271.9 to −196.1)	−192.5 (−225.3 to −159.6)		−252.3 (−300.6 to −204.0)	−226.6 (−267.0 to −186.3)
P value‖			<0.001			<0.001
Volume of menstrual blood loss at 3 mo — ml						
No. of women with data	85	83	172	78	72	157
Change from baseline — least-squares mean (95% CI)	6.1 (−24.1 to 36.2)	−234.7 (−265.0 to −204.5)	−192.2 (−213.4 to −170.9)	−14.2 (−37.0 to 8.6)	−211.1 (−234.6 to −187.6)	−200.3 (−216.4 to −184.2)
Difference from placebo (95% CI)		−240.8 (−283.5 to −198.1)	−198.2 (−235.1 to −161.3)		−196.9 (−229.7 to −164.1)	−186.1 (−214.0 to −158.2)
P value‖			<0.001			<0.001
Women with baseline hemoglobin level ≤10.5 g/dl and increase from baseline of >2 g/dl at 6 mo						
Percentage of women — no./total no. (%)	5/31 (16)	27/41 (66)	32/52 (62)	5/24 (21)	10/25 (40)	24/48 (50)
Difference from placebo (95% CI)		49.7 (30.27 to 69.18)	45.4 (26.90 to 63.92)		19.2 (−6.0 to 44.3)	29.2 (7.6 to 50.7)

P value¶			<0.001				0.02
Volume of menstrual blood loss at 1 mo — ml							
No. of women with data	95	97	187	88	83		175
Change from baseline — least-squares mean (95% CI)	−19.0 (−50.6 to 12.6)	−209.0 (−240.3 to −177.8)	−135.2 (−157.6 to −112.7)	−2.1 (−30.2 to 26.1)	−196.6 (−225.6 to −167.6)		−127.0 (−146.9 to −107.1)
Difference from placebo (95% CI)		−190.0 (−234.5 to −145.6)	−116.2 (−154.9 to −77.4)		−194.5 (−235.0 to −154.1)		−125.0 (−159.5 to −90.4)
P value‖			<0.001				<0.001

* Outcomes are listed in the order of hierarchical statistical testing.
† The final month was defined as the last 28 days before and including the last treatment period visit date. If data on menstrual blood loss (measured with the use of the alkaline hematin method) that could be evaluated were available between the last treatment period visit date and the last dose date, then the last dose date was used. The missing data on menstrual blood loss in the final month were imputed with the use of multiple imputation.
‡ The P value was based on an analysis of covariance model with treatment as the main effect and baseline volume of menstrual blood loss as a covariate in each data set from multiple imputation.
§ Suppression of bleeding indicated no bleeding, although there may have been spotting.
¶ The P value was based on the chi-square test (or Fisher's exact test if ≥20% of the cells in the categorical table had an expected cell count of <5).
‖ The P value was based on a mixed model for repeated measures with treatment, month, and an interaction between treatment and month as fixed-effect factors and baseline volume of menstrual blood loss as a covariate in the comparison of each elagolix-with-add-back group with placebo.

life. The least-squares mean (±SE) change in women who received elagolix with add-back therapy was 38.0±1.62 in UF-1 and 42.0±1.62 in UF-2 (as compared with 10.9±2.27 and 6.5±2.32, respectively, in women who received placebo) (Fig. S6).

SAFETY

More than 60% of the women in each trial group reported at least one adverse event. The incidence of any adverse event was significantly higher among women who received elagolix alone in UF-1 (P<0.001) and among those who received elagolix plus add-back therapy in UF-2 (P<0.05) than among those who received placebo (Table 3). Most adverse events were considered by the investigators to be mild or moderate in severity. Serious and severe adverse events are listed in Tables S5 and S6, respectively. All serious adverse events that were reported in the elagolix groups were resolved by the end of the trial. Hot flushes were significantly more common with elagolix plus add-back therapy (20.4% and 19.6%, respectively, in UF-1 and UF-2) and elagolix alone (64.4% and 43%) than with placebo (8.8% and 4%); in UF-1 and UF-2, night sweats were significantly more common with elagolix alone (26.9% and 25%, respectively) than with placebo (2.9% and 5%, respectively) (Table 3). Details regarding the severity profiles of hot flushes and night sweats each month and for the entire treatment course are shown in Table S7 and Figure S7. In addition, in UF-1, metrorrhagia was significantly more common among women who received elagolix plus add-back therapy than among those who received placebo (6.3% vs. 0%). No deaths were reported during the treatment period in either trial. Two pregnancies in the placebo group (one live birth and one spontaneous abortion) and one in the elagolix-alone group (an ectopic pregnancy) were reported during the treatment period in the two trials (Table S8).

There were no significant differences in the trials between the women who received elagolix with add-back therapy and those who received placebo with respect to the mean percent change in bone mineral density in the lumbar spine, total hip, or femoral neck from baseline to 6 months (Fig. 2). Although not all patients had a decrease in bone mineral density, the mean percent decrease in bone mineral density was significantly

Table 3. Adverse Events.*

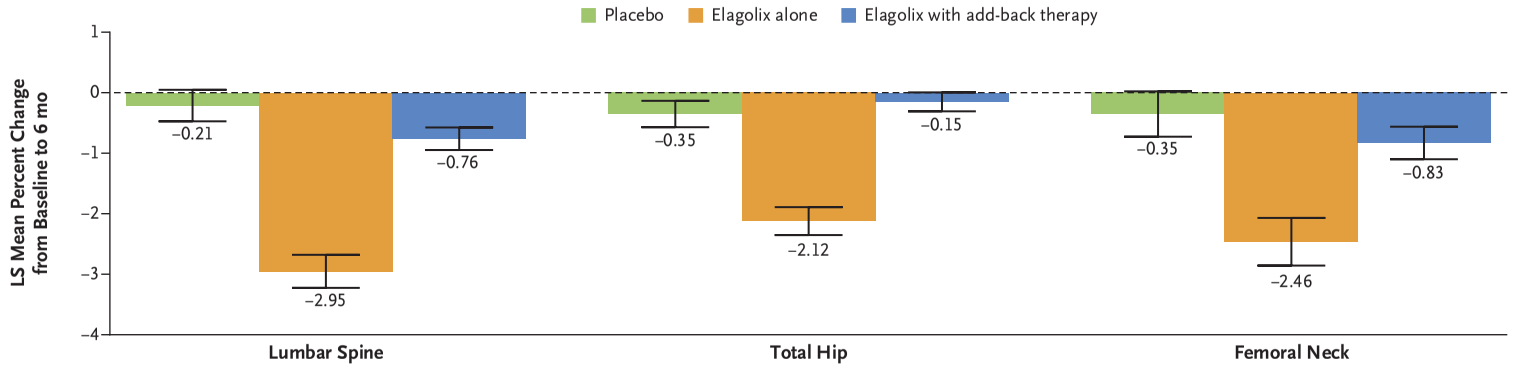
Event	Elaris UF-1			Elaris UF-2		
	Placebo (N=102)	Elagolix Alone (N=104)	Elagolix with Add-Back Therapy (N=206)	Placebo (N=94)	Elagolix Alone (N=95)	Elagolix with Add-Back Therapy (N=189)
	number (percent)					
Adverse events						
Any adverse event	71 (69.6)	94 (90.4)†	140 (68.0)	59 (63)	72 (76)	143 (75.7)‡
Any serious adverse event§	5 (4.9)	3 (2.9)	3 (1.5)	1 (1)	4 (4)	7 (3.7)
Any severe adverse event¶	4 (3.9)	9 (8.7)	19 (9.2)	6 (6)	11 (12)	17 (9.0)
Any adverse event leading to trial-drug discontinuation	8 (7.8)	10 (9.6)	22 (10.7)	5 (5)	12 (13)	16 (8.5)
Adverse events in ≥5% of women who received elagolix with add-back therapy in either trial						
Hot flushes	9 (8.8)	67 (64.4)†	42 (20.4)‖	4 (4)	41 (43)†	37 (19.6)†
Nausea	10 (9.8)	7 (6.7)	23 (11.2)	9 (10)	4 (4)	14 (7.4)
Headache	9 (8.8)	17 (16.3)	17 (8.3)	5 (5)	13 (14)	20 (10.6)
Night sweats	3 (2.9)	28 (26.9)†	14 (6.8)	5 (5)	24 (25)†	20 (10.6)
Fatigue	2 (2.0)	1 (1.0)	14 (6.8)	5 (5)	3 (3)	10 (5.3)
Dysmenorrhea	4 (3.9)	1 (1.0)	13 (6.3)	6 (6)	0‡	7 (3.7)
Metrorrhagia	0	1 (1.0)	13 (6.3)‖	1 (1)	0	7 (3.7)
Nasopharyngitis	4 (3.9)	6 (5.8)	10 (4.9)	8 (9)	4 (4)	10 (5.3)
Decreased libido	0	5 (4.8)	7 (3.4)	2 (2)	3 (3)	10 (5.3)
Urinary tract infection	3 (2.9)	3 (2.9)	3 (1.5)	5 (5)	2 (2)	12 (6.3)

* All adverse events were summarized with the use of the *Medical Dictionary for Regulatory Activities*, version 21.0, and are listed in descending order of incidence, starting with women who received elagolix with add-back therapy, then women who received elagolix alone, and then women who received placebo in Elaris UF-1, followed by women who received elagolix with add-back therapy, then women who received elagolix alone, and then women who received placebo in Elaris UF-2.
† P<0.001 for the comparison with placebo, according to Fisher's exact test.
‡ P<0.05 for the comparison with placebo, according to Fisher's exact test.
§ Serious adverse events were defined as life-threatening, resulting in hospitalization or medical or surgical intervention to prevent a serious outcome, or resulting in persistent disability or death.
¶ The severity of each adverse event was rated by the investigators as mild, moderate, or severe.
‖ P<0.01 for the comparison with placebo, according to Fisher's exact test.

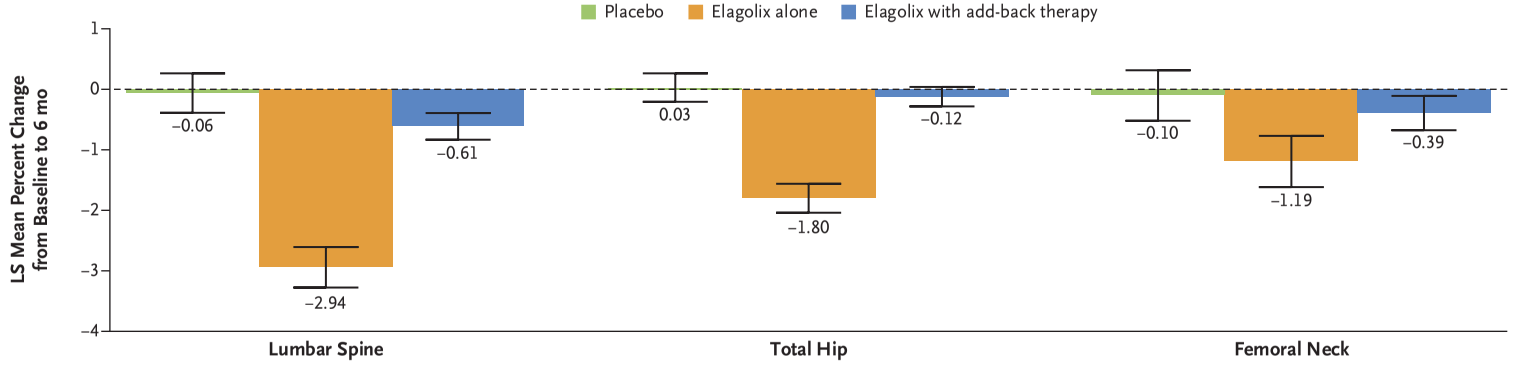
smaller with elagolix plus add-back therapy than with elagolix alone in all locations, except the femoral neck in UF-2. (Categorical assessments of changes in bone mineral density are summarized in Figure S8.)

Both elagolix groups had a mean increase from baseline in serum lipid levels (i.e., total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels), relative to placebo. These increases generally occurred within the first 3 months after initiation of treatment and then stabilized (Fig. S9).

The mean levels of liver aminotransferases, alkaline phosphatase, and bilirubin from baseline to 6 months were not significantly higher in the group of women who received elagolix plus add-back therapy than in the group of women who received placebo (Fig. S10). Across both trials, 10 women — all in the elagolix groups (6 in UF-1: 3 [2.9%] in elagolix alone and 3 [1.5%] in elagolix with add-back therapy; 4 in UF-2: 1 [1%]



Difference from placebo — % (95% CI)		−2.75 (−3.49 to −2.01)	−0.55 (−1.18 to 0.08)		−1.77 (−2.39 to −1.14)	0.20 (−0.33 to 0.73)		−2.10 (−3.17 to −1.04)	−0.48 (−1.39 to 0.43)
Difference between elagolix groups — % (95% CI)		−2.19 (−2.84 to −1.54)			−1.97 (−2.51 to −1.42)			−1.63 (−2.57 to −0.69)	
No. of women	82	74	159	82	74	159	82	74	159



Difference from placebo — % (95% CI)		−2.88 (−3.80 to −1.96)	−0.55 (−1.33 to 0.23)		−1.82 (−2.48 to −1.17)	−0.15 (−0.71 to 0.41)		−1.08 (−2.26 to 0.09)	−0.29 (−1.29 to 0.71)
Difference between elagolix groups — % (95% CI)		−2.33 (−3.12 to −1.54)			−1.67 (−2.24 to −1.11)			−0.80 (−1.80 to 0.21)	
No. of women	68	65	147	68	66	146	68	66	146

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

At 6 months, all the differences in the percent change in bone mineral density between the group of women who received elagolix with add-back therapy and the group of women who received placebo were not significant, whereas the differences in the percent change in bone mineral density between the elagolix-alone group and the placebo group were significant, except for the between-group difference at the femoral neck in Elaris UF-2. Statistical comparisons between the trial groups were analyzed with the use of an analysis of covariance model, with treatment as the main effect and the baseline bone mineral density value as a covariate. The I bars indicate 95% confidence intervals. LS denotes least squares.

in elagolix alone and 3 [1.6%] in elagolix with add-back therapy) — had elevations in liver aminotransferases that were greater than 3 times the upper limit of the normal range; none of these women had concurrent elevations in bilirubin levels. All elevated aminotransferase levels returned to the normal range, with the decline seen within 1 to 4 months after peak values, regardless of whether the women continued to receive elagolix (8 women) or not (2 women).

Despite cycle-related differences, there was a decrease in mean endometrial thickness among women who received elagolix plus add-back therapy at 6 months (Fig. S11). No cases of endometrial hyperplasia or cancer were detected on endometrial biopsies in the elagolix groups; there was one case of hyperplasia in the placebo group (Table S9). No new ovarian cysts were reported during elagolix treatment (Table S10).

DISCUSSION

In two identical, double-blind, randomized, placebo-controlled, 6-month phase 3 trials involving women with heavy menstrual bleeding associated with uterine fibroids, menstrual blood loss was significantly lower among women who received elagolix with add-back therapy than among those who received placebo. Elagolix with add-back therapy was associated with a significantly greater mean reduction in menstrual blood loss from baseline to the final month, a higher percentage of women with suppression of bleeding, a greater mean reduction in menstrual blood loss from baseline to 6 months and 3 months, a higher percentage of women with a low baseline hemoglobin level (≤10.5 g per deciliter) who had an increase in the hemoglobin level that was greater than 2 g per deciliter at 6 months, and a greater mean reduction in menstrual blood loss from baseline to 1 month. Findings with respect to uterine volume (measured by means of magnetic resonance imaging) and improvements in quality of life were consistent with the effects on the primary and secondary end points.

Elagolix was associated with a low incidence of serious adverse events; none of these events were related to drug-induced liver injury, and there were no clinically meaningful endometrial abnormalities. Elagolix with add-back therapy attenuated decreases in bone mineral density seen with elagolix alone. In both trials, the mean percent changes in bone mineral density in all measured sites did not significantly differ between the groups of women who received elagolix with add-back therapy and those who received placebo. The decreases from baseline in bone mineral density that occurred in women who received elagolix alone were significantly greater than in those who received elagolix with add-back therapy and also significantly greater than in those who received placebo (except at the femoral neck in UF-2). The attenuation of hypoestrogenic effects in women who received elagolix plus add-back therapy as compared with those who received elagolix alone is consistent with the results of other trials of GnRH analogues.[28,29] Because of the mechanism of action, hot flushes still occurred in a higher percentage of women who received elagolix with add-back therapy than in those who received placebo.

These large prospective trials involving women with uterine fibroids included a high percentage of black women, who are at higher risk for uterine fibroids and tend to have more severe symptoms than white women. The alkaline hematin method was used to quantify all bleeding end points.[3-5,33-39] The present data inform the efficacy and safety of this treatment through 6 months; the 6-month extension trial (up to 12 months of treatment) was conducted to provide more information on longer-term benefits and risks of elagolix with add-back therapy, as was previously shown in extension studies of elagolix in women with endometriosis-associated pain.[40] Since the trials were designed primarily to compare elagolix plus add-back therapy with placebo and prespecified a comparison of the two elagolix groups only with respect to bone mineral density, we cannot make conclusions regarding elagolix with add-back therapy as compared with elagolix alone with respect to the effects on other outcomes.

In both trials reported here, the risk of heavy menstrual bleeding among premenopausal women with uterine fibroids was significantly lower among women who received elagolix, an oral GnRH antagonist, at a dose of 300 mg twice daily with add-back therapy for 6 months than among those who received placebo. As compared with elagolix alone, add-back therapy attenuated decreases in bone mineral density associated with elagolix alone.

Supported by AbbVie.

Dr. Schlaff reports receiving consulting fees from Antares Pharma and grant support and consulting fees from AbbVie; Dr. Ackerman, receiving grant support from Myovant Sciences, Watson Laboratories, and AbbVie; Dr. Al-Hendy, receiving consulting fees from AbbVie, Allergan, Bayer, Myovant Sciences, and MD Stem Cells and holding patent 9,790,562 B2 on methods for new diagnostic methods and therapeutic agents for uterine sarcoma; Dr. Archer, receiving grant support from Actavis, Glenmark Pharmaceuticals, Merck, ObsEva, Myovant Sciences, Shionogi, and AbbVie, grant support and travel support from Bayer Healthcare, and grant support, honoraria, lecture fees, and travel support from Endoceutics and TherapeuticsMD; Dr. Barnhart, receiving consulting fees from Bayer and AbbVie; Dr. Bradley, receiving grant support and advisory board fees from Bayer, advisory board fees from Medtronics and AbbVie, and fees for serving on a data and safety monitoring board from Gynesonics; Dr. Carr, receiving grant support from Synteract and AbbVie and fees for serving on a data and safety monitoring board from Repros Therapeutics; Dr. Feinberg, receiving consulting fees from AbbVie, Natera, and CooperSurgical; Dr. Hurtado, receiving grant support from Myovant Sciences, Bayer, ObsEva, Femasys, Ferring Pharmaceuticals, Allergan, Amgen, and TherapeuticsMD, grant support and fees for serving on a speakers bureau from AbbVie, and fees for serving on a speakers bureau from Merck; Dr. Kim, receiving consulting fees from AbbVie; Dr. Liu, being employed by and having an equity interest in AbbVie; Dr. Mabey, receiving grant support from AbbVie; Dr. Owens, being employed by AbbVie; Dr. Poindexter, receiving grant support from AbbVie, Bayer, Allergan, and ObsEva; Dr. Puscheck, receiving grant support from Bayer, Ferring Pharmaceuticals, and ObsEva, and fees for serving on a clinical events committee from Femasys; Dr. Rodriguez-Ginorio, serving as principal investigator for AbbVie; Dr. Simon, receiving grant support and consulting fees from Endoceutics and Palatin Technologies, grant support from Ipsen, Symbio, Viveve, and Hologic, consulting fees and nonfinancial support (editorial review and writing assistance, statistical support, or database access) from CEEK and Sprout Pharmaceuticals, consulting fees from Ascendia Pharmaceuticals, Dare Bioscience, KaNDy Therapeutics, Mitsubishi Tanabe Pharma, and Sanofi, fees for serving on a data and safety monitoring board from Covance, grant support, consulting fees, and fees for serving on a speakers bureau from Duchesnay, consulting fees, fees for serving on a speakers bureau, and nonfinancial support from Shionogi, grant support, consulting fees, fees for serving on a speakers bureau, and nonfinancial support from TherapeuticsMD and AMAG Pharmaceuticals, fees for serving on a speakers bureau from Novo Nordisk, grant support, consulting fees, and nonfinancial support from Myovant Sciences, Allergan, ObsEva, and Bayer, and consulting fees and lecture fees from AbbVie; Dr. Soliman, being employed by and owning stock in AbbVie; Dr. Stewart, receiving consulting fees from Bayer, Welltwigs, AbbVie, and Allergan, fees for serving on a steering committee from Myovant Sciences, fees for development of educational content from Med Learning Group, and holding patent 6440445 on Methods and Compounds for Treatment of Abnormal Uterine Bleeding; Dr. Watts, receiving consulting fees from AbbVie, consulting fees and lecture fees from Amgen, and lecture fees from Radius Health; and Dr. Muneyyirci-Delale, receiving grant support from Bayer, ObsEva, and Ferring Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank all the women and the trial investigators who participated in these clinical trials; all vendors who supported the trials; and AbbVie employees, including the trial team for their operational support of these trials; Jeanie K. Meckes, Ph.D., and Amy Spiegel, Ph.D., for assistance in medical writing; Kristof Chwalisz, M.D., Ph.D., for contributions to the uterine fibroid program; James W. Thomas, M.S., for contributions to the trial design and statistical interpretation; and Yanping Luo, Ph.D., for contributions to imaging applications.

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