

Efficacy and safety of elagolix with add-back therapy in women with uterine fibroids and coexisting adenomyosis

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Objective: To determine if coexisting adenomyosis limits the efficacy of elagolix, an oral gonadotropin-releasing hormone antagonist, with hormonal add-back therapy in reducing heavy menstrual bleeding in women with uterine fibroids.

Design: Pooled analysis of two identical, double-blind, randomized, placebo-controlled, 6-month phase 3 trials (Elaris Uterine Fibroids [UF]-1 and UF-2).

Setting: A total of 153 gynecological clinical care settings in the United States and Canada.

Patient(s): Premenopausal women (18–51 years) with >80 mL of menstrual blood loss (MBL)/cycle and uterine fibroids with and without coexisting adenomyosis diagnosed by ultrasound and/or magnetic resonance imaging at baseline.

Intervention(s): Participants were randomized 1:1:2 to placebo, elagolix 300 mg twice daily alone, or elagolix 300 mg twice daily with estradiol 1 mg/norethindrone acetate 0.5 mg once daily.

Main Outcome Measure(s): The primary endpoint was the proportion of women who had <80 mL of MBL during the final month and ≥ 50% reduction in MBL from baseline to the final month. Adverse events were monitored.

Result(s): Of 786 women treated across the two trials, 16% (126 women) had coexisting adenomyosis. Among this subset, a significantly greater proportion of women who received elagolix with add-back therapy (77.1% [95% confidence interval, 66.2, 88.0]) met both primary endpoint criteria compared with women who received placebo (12.2% [95% confidence interval, 1.0, 23.4]). Adverse

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events most frequently reported in the elagolix with add-back adenomyosis subset were hot flushes (18.3%), nausea (11.7%), and night sweats (8.3%).

Conclusion(s): Elagolix with add-back therapy significantly reduced heavy menstrual bleeding in women with uterine fibroids and coexisting adenomyosis, suggesting that elagolix efficacy was not adversely affected by the presence of adenomyosis (Elaris UF-1 and UF-2 [ClinicalTrials.gov](https://clinicaltrials.gov) numbers, NCT02654054 and NCT02691494). (Fertil Steril Rep® 2021;2:338–46. ©2021 by American Society for Reproductive Medicine.)

Key Words: Adenomyosis, elagolix, uterine fibroids

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Adenomyosis, a condition in which endometrial glands and stroma are present within the myometrium, commonly coexists with uterine fibroids (leiomyomas) (1, 2). Both adenomyosis and uterine fibroids, when symptomatic, present with similar symptoms, including heavy menstrual bleeding, which can lead to anemia (3–5). Their associated symptoms of bleeding and pain can have a major impact on a woman's quality of life (6–8). While there are a number of surgical and procedural alternatives to hysterectomy for uterine fibroids including myomectomy and uterine artery embolization, there are limited alternatives to hysterectomy for adenomyosis (9–12). Hormonal medical treatments such as oral contraceptives, progestins, levonorgestrel-releasing intrauterine system, danazol, and gonadotropin-releasing hormone agonists may provide symptomatic relief (9, 10); however, there are limited randomized controlled trial data that demonstrate the long-term efficacy of these agents in women with uterine fibroids and coexisting adenomyosis. Therefore, there is a need for a medical treatment option as an alternative to surgery that provides long-term, safe, and effective management of heavy menstrual bleeding for women with uterine fibroids and coexisting adenomyosis.

Elagolix is an oral, nonpeptide gonadotropin-releasing hormone antagonist that results in rapid, reversible, and dose-dependent suppression of gonadotropins and ovarian sex steroids (13, 14). In two identical phase 3 trials, the efficacy of elagolix 300 mg twice daily (BID) with hormonal add-back therapy (estradiol 1 mg/norethindrone acetate 0.5 mg once daily [QD]) was superior to placebo in reducing heavy menstrual bleeding in women with uterine fibroids (15). Because a subset of these women with uterine fibroids had coexisting adenomyosis at baseline (126 women, 16%), we evaluated the efficacy in reducing heavy menstrual bleeding in this subset of women who had uterine fibroids and coexisting adenomyosis compared with to placebo and the safety of elagolix with add-back therapy in this same population.

MATERIALS AND METHODS

Participants and Study Design

This analysis included pooled data from two identical, double-blind, randomized, placebo-controlled, 6-month phase 3 trials (Elaris Uterine Fibroids [UF]-1 and UF-2; NCT02654054 and NCT02691494). Elaris UF-1 was conducted at 76 sites in the United States (including Puerto Rico) from December 2015 through December 2018, and Elaris UF-2 was

conducted at 77 sites in the United States and Canada from February 2016 through January 2019. A total of 790 women were randomized and treated across both trials. Of the 790 women, 4 individuals were randomized and treated before the trial registration date on [ClinicalTrials.gov](https://clinicaltrials.gov) because of administrative error and were, therefore, excluded from this current analysis.

Information on the eligibility criteria and study design has been previously published (15). Briefly, eligible participants were premenopausal women aged 18–51 years at the time of screening who had an ultrasound-confirmed diagnosis of uterine fibroids (intramural, submucosal nonpedunculated fibroid with longest diameter ≥ 2 cm or subserosal fibroid ≥ 4 cm or multiple fibroids with a total uterine volume of ≥ 200 to $\leq 2,500$ cm³) and heavy menstrual bleeding demonstrated by >80 mL of menstrual blood loss (MBL) per cycle for at least two separate cycles as measured by the alkaline hematin method. This current analysis included women with uterine fibroids and heavy menstrual bleeding who had radiologic evidence of coexisting adenomyosis of any type (i.e., focal, diffuse dominant [$>50\%$ of the myometrium], or diffuse nondominant) at baseline (16).

The presence or absence of coexisting adenomyosis was evaluated by transvaginal ultrasound in all participants and additionally by magnetic resonance imaging (MRI) in a subset of participants who elected to have an optional MRI. In the trials, if a participant had both ultrasound and MRI results at baseline and they differed ($n = 83$), the MRI results were used to determine the presence or absence of coexisting adenomyosis. If the transvaginal ultrasound results were unevaluable ($n = 3$), MRI only was used to diagnose. Conversely, if a participant did not have baseline MRI results available ($n = 16$), the ultrasound results were used to determine the presence or absence of coexisting adenomyosis. The remainder of subjects with adenomyosis were identified by both ultrasound and MRI ($n = 24$). Images for both ultrasound and MRI were acquired using standardized image acquisition procedures. Further details on the number of patients diagnosed with either ultrasound or MRI in each treatment group are shown in [Supplemental Table 1](#) (available online). All results were prospectively read and analyzed by independent centralized radiologists who were instructed to determine cardinal diagnostic features of adenomyosis (e.g., asymmetric thickening of the myometrium, myometrial cysts, linear striations radiating out from the endometrium, loss of a clear endomyometrial border, and increased myometrial heterogeneity) (1, 17).

The trials included a washout period of hormonal medication, screening period of 2.5–3.5 months, 6-month treatment period, and 12-month follow-up period (or a corresponding extension study). This article presents results from the 6-month treatment period of the trials. Women were randomized (1:1:2) at the start of the 6-month treatment period to receive either placebo, elagolix 300 mg BID alone, or elagolix 300 mg BID with hormonal add-back therapy (estradiol 1 mg/norethindrone acetate 0.5 mg QD). These trials primarily assessed the efficacy of elagolix with add-back therapy. Although elagolix alone was efficacious in reducing heavy menstrual bleeding associated with uterine fibroids including those with adenomyosis, its purpose was as a reference group to characterize the impact of add-back therapy on the safety/tolerability of elagolix, and consequently, it was not included in this subset analysis for efficacy. Subset analysis was performed to determine whether the presence or absence of adenomyosis influenced the efficacy of elagolix with add-back therapy in women with uterine fibroids. Additionally, outcomes from the overall pooled population were included as a reference for whether the efficacy of elagolix in women with adenomyosis was similar to the overall population.

These trials were conducted in the United States and Canada and in accordance with the International Council for Harmonisation guidelines and applicable regulations and ethical principles of the Declaration of Helsinki. The trial protocols were approved by the Schulman Institutional Review Board for central sites and by the institutions' ethics committee for all other sites. All women provided written informed consent.

Endpoints and Assessments

The primary endpoint was the proportion of women who had both <80 mL of MBL during the final month and $\geq 50\%$ reduction in MBL from baseline to the final month (1, 15). Final month was defined as the last 28 days before and including the last treatment period visit date (if data on MBL [measured using 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). Women who prematurely discontinued the study drug because of adverse events, lack of efficacy, or required surgery or invasive intervention for uterine fibroid treatment were considered to have not met the primary endpoint even if they met the two bleeding criteria of the primary endpoint. Other endpoints objectively assessed in this subset analysis were the mean change in MBL from baseline to the final month and the proportion of women with suppression of bleeding (defined as no bleeding but spotting allowed) at the final month (15). In addition, the proportion of women with amenorrhea at the final month, mean change in uterine volume from baseline to month 6, and mean change in the Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL) questionnaire symptom severity subscale and health-related quality of life total scores (scores range from 0 to 100) were quantified. Higher symptom severity scores indicate increased severity, while higher health-related quality of life total scores (the sum of scores on six subscales:

concern, activities, energy and mood, control, self-consciousness, and sexual function) indicate better quality of life. In addition, treatment-emergent adverse events were assessed.

Statistical Analysis

This study included all women who underwent randomization and received at least one dose of elagolix or placebo, including those who prematurely discontinued or withdrew consent. The adenomyosis subset was defined as those who were diagnosed with uterine fibroids and coexisting adenomyosis by ultrasound and/or MRI at baseline. For the ANOVA model, the chi-square test was used to determine significance for categorical variables. Analyses for each of the endpoints were performed for the overall pooled study population and repeated for the adenomyosis subset and separately for women without an adenomyosis diagnosis at baseline. For demographics and baseline characteristics, the chi-square test for categorical variables and one-way ANOVA for continuous variables were used to compare women with uterine fibroids coexisting with adenomyosis at baseline and women with uterine fibroids without an adenomyosis diagnosis at baseline. For each subset, statistical comparisons between each elagolix treatment group and placebo were made for the primary endpoint using a logistic regression model with treatment and study as the main effects and baseline MBL as a covariate (missing final month data were imputed using multiple imputation), the mean change in MBL from baseline to the final month using an ANCOVA model with treatment and study (Elaris 1 and 2) as the main effects and baseline MBL volume as a covariate (data were imputed from the primary endpoint analysis), the proportion of women with suppression of bleeding at the final month and the proportion with amenorrhea at the final month using a Cochran-Mantel-Haenszel test with the study as a stratification factor, and the mean changes from baseline to month 6 in uterine volume and UFS-QOL scores using an ANCOVA model with treatment as the main effect and baseline as a covariate. All statistical tests were performed using SAS software (version 9.4) with a two-sided significance level of 0.05 and a confidence interval (CI) of 95%.

RESULTS

Participants

Of the 786 women randomized and treated in one of the two phase 3 trials, 126 (16%) were diagnosed with coexisting adenomyosis by ultrasound and/or MRI at baseline; 36.5% had focal adenomyosis, 42.9% had dominant diffuse, and 20.6% had nondominant diffuse. Of these 126 women, the proportions of those who prematurely discontinued the study drug were similar across treatment groups (placebo, 23.5%; elagolix alone, 15.6%; elagolix with add-back therapy, 20.0%) (Table 1). In addition, similar proportions of women prematurely discontinued among women without an adenomyosis diagnosis at baseline and the overall pooled study population.

Women in the adenomyosis subset were significantly older than women without an adenomyosis diagnosis at

TABLE 1

Patient disposition, demographics, and baseline characteristics.

Baseline characteristic	Women with uterine fibroids and coexisting adenomyosis at baseline	Women with uterine fibroids without adenomyosis diagnosis at baseline	Overall pooled study population
Randomized and treated, n	126	660	786
Placebo	34	161	195
Elagolix alone	32	167	199
Elagolix with add-back therapy	60	332	392
Discontinued, n (%)			
Placebo	8 (23.5)	32 (19.9)	40 (20.5)
Elagolix alone	5 (15.6)	44 (26.3)	49 (24.6)
Elagolix with add-back therapy	12 (20.0)	71 (21.4)	83 (21.2)
Age, years	43.7 (5.0)	42.1 (5.4) ^a	42.4 (5.4)
Race, n (%)			
Black/African American	80 (64.0)	449 (68.1)	529 (67.5)
Other	45 (36.0)	210 (31.9)	255 (32.5)
Missing	1	1	2
BMI, kg/m ²	32.6 (6.3)	33.8 (7.4)	33.6 (7.3)
MBL, mL	215.7 (125.4)	244.7 (164.3)	240.0 (159.0)
Uterine volume by TAU/TVU, cm ³	374.2 (306.5)	525.2 (429.8) ^b	501.0 (416.1)
Average fibroid volume by TAU/TVU, cm ³	33.0 (59.8)	61.2 (96.4) ^a	56.8 (92.1)
Primary fibroid volume by TAU/TVU, cm ³	45.1 (69.2)	86.2 (130.1) ^b	79.6 (123.4)
Number of pregnancies, numbers (%) of subjects			
0	2 (1.7)	2 (0.4)	4 (0.6)
1	12 (10.3)	110 (20.0)	122 (18.3)
2	32 (27.6)	141 (25.7)	173 (26.0)
3	25 (21.6)	121 (22.0)	146 (22.0)
4	17 (14.7)	77 (14.0)	94 (14.1)
≥5	28 (24.1)	98 (17.9)	126 (18.9)
Number of full-term pregnancies			
0	17 (14.7)	95 (17.3)	112 (16.8)
1	28 (24.1)	141 (25.7)	169 (25.4)
2	33 (28.4)	161 (29.3)	194 (29.2)
3	25 (21.6)	99 (18.0)	124 (18.6)
4	10 (8.6)	37 (6.7)	47 (7.1)
≥5	3 (2.6)	16 (2.9)	19 (2.9)
Presence of adenomyosis at baseline	126 (100.0)	0	126 (16.0)
Focal	46 (36.5)		46 (5.9)
Dominant diffuse	54 (42.9)		54 (6.9)
Nondominant diffuse	26 (20.6)		26 (3.3)
UFS-QOL scores			
Symptom severity	65.8 (19.6)	59.2 (22.0) ^a	60.2 (21.7)
HRQL total	34.7 (20.6)	44.3 (23.3) ^b	42.8 (23.2)

Note: Four women who were randomized and treated before the trial registration date were excluded from this analysis. Data are presented as mean (SD) unless otherwise specified. For UFS-QOL scores, a higher symptom severity score indicates worse symptom severity, while a higher HRQL total score indicates better health-related quality of life. BID = twice daily; BMI = body mass index; HRQL = health-related quality of life; MBL = menstrual blood loss; TAU/TVU = transabdominal ultrasound/transvaginal ultrasound; UFS-QOL = Uterine Fibroid Symptom and Health-Related Quality of Life.

Statistical significance comparing between women with uterine fibroids coexisting with adenomyosis at baseline and women with uterine fibroids without an adenomyosis diagnosis at baseline was performed using the chi-square test for categorical variables and one-way ANOVA for continuous variables, indicated by:

^a $P < .01$

^b $P < .001$.

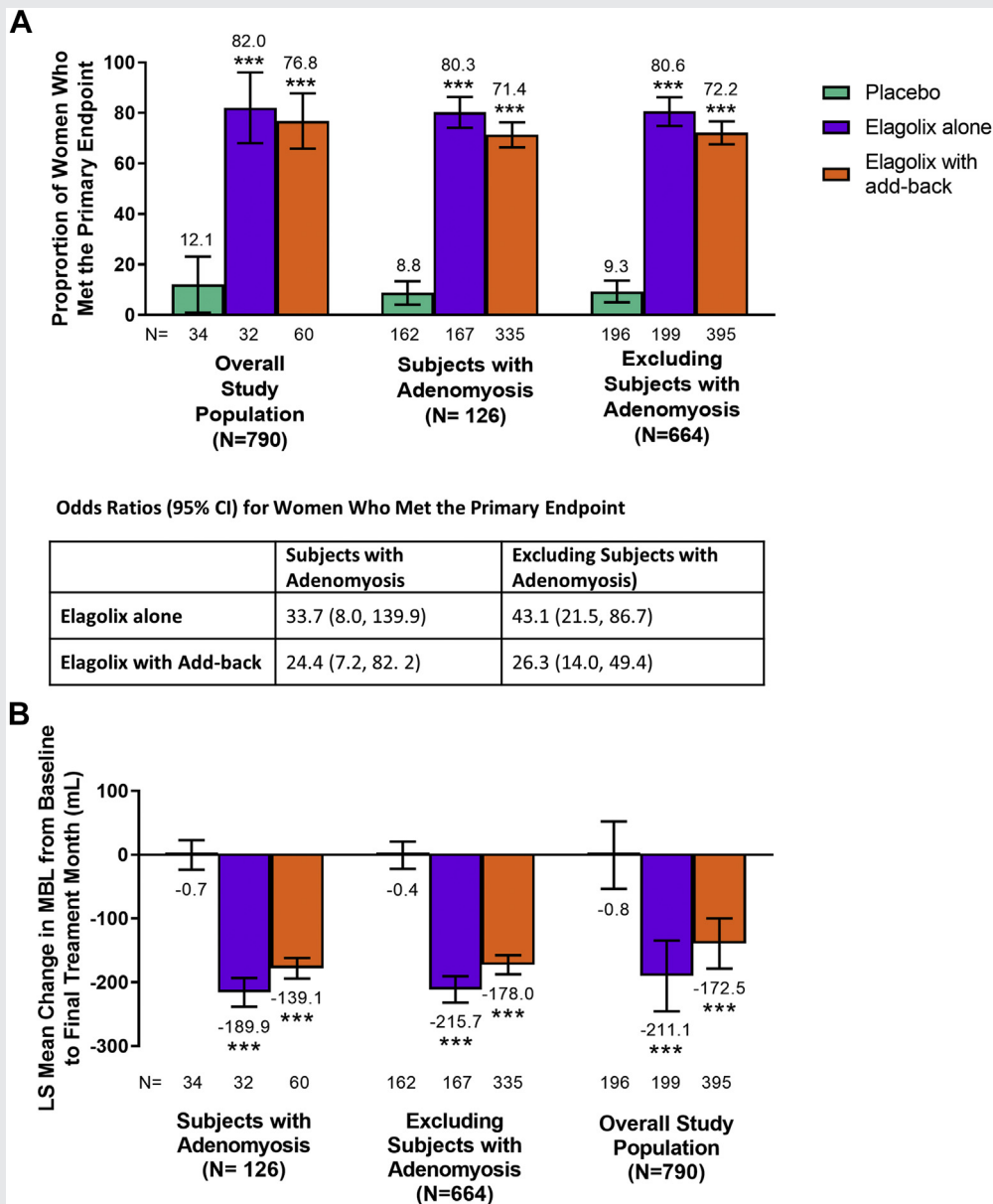
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baseline ($P < .05$) (Table 1). While there were no notable differences observed in the mean body mass index and MBL at baseline, women in the adenomyosis subset had statistically significantly smaller mean uterine and fibroid (average and largest) volumes as well as significantly worse symptom severity and health-related quality of life on the basis of the UFS-QOL domain scores ($P < .01$) than women without an adenomyosis diagnosis at baseline (Table 1). There were no notable differences observed in gravidity and parity among women with and without an adenomyosis diagnosis at baseline (Table 1).

Menstrual Bleeding Endpoints

Women who had uterine fibroids and coexisting adenomyosis at baseline had similar reduction in menstrual bleeding, as measured by multiple endpoints, to those without an adenomyosis diagnosis at baseline with elagolix with add-back treatment. Specifically, a significantly greater proportion of those who received elagolix with add-back therapy (76.8% [95% CI, 65.8, 87.8]) achieved the 2 bleeding criteria of the primary endpoint compared with those who received placebo (12.1% [95% CI, 1.0, 23.2]) ($P < .001$); these results were similar to those without an adenomyosis diagnosis at baseline

FIGURE 1



Primary endpoint: reduction in heavy menstrual bleeding. Four women who were randomized and treated before the trial registration date were excluded from this analysis. Error bars indicate 95% confidence interval. Statistical significance compared with placebo was by pooling the results from a logistic regression model including treatment and study as the main effects and baseline MBL volume as a covariate in each data set from multiple imputation. * $P < .05$, ** $P < .01$, and *** $P < .001$. 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 using 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. Statistical comparisons were not made between adenomyosis subsets. LS = least squares; MBL = menstrual blood loss.

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and the overall pooled study population that included all women with heavy menstrual bleeding associated with uterine fibroids (Fig. 1A). Compared with women who received placebo, those in this adenomyosis subset who received elagolix with add-back therapy had a significantly greater

mean reduction in MBL from baseline to the final month ($P < .001$), as did women without an adenomyosis diagnosis at baseline and the overall pooled study population (Fig. 1B). Additionally, a significantly greater proportion of women in the adenomyosis subset treated with elagolix plus

TABLE 2

Secondary and other endpoints related to bleeding, uterine volume, and fibroid-related quality of life.

Endpoint measured	Placebo			Elagolix 300 mg BID			Elagolix 300 mg BID + add-back therapy		
	Women with uterine fibroids and coexisting adenomyosis (N = 34)	Women with uterine fibroids without adenomyosis diagnosis at baseline (N = 161)	Overall pooled study population (N = 195)	Women with uterine fibroids and coexisting adenomyosis (N = 32)	Women with uterine fibroids without adenomyosis diagnosis at baseline (N = 167)	Overall pooled study population (N = 199)	Women with uterine fibroids and coexisting adenomyosis (N = 60)	Women with uterine fibroids without adenomyosis diagnosis at baseline (N = 332)	Overall pooled study population (N = 392)
Proportion of women with suppression of bleeding ^a at the final month ^b	1/30 (3.3)	6/145 (4.1)	7/175 (4.0)	23/28 (82.1) ^f	128/147 (87.1) ^f	151/175 (86.3) ^f	35/55 (63.6) ^f	172/297 (57.9) ^f	207/352 (58.8) ^f
Proportion of women with amenorrhea at the final month ^b	1/30 (3.3)	6/145 (4.1)	7/175 (4.0)	23/28 (82.1) ^f	121/147 (82.3) ^f	144/175 (82.3) ^f	34/55 (61.8) ^f	143/297 (48.1) ^f	177/352 (50.3) ^f
Mean change from baseline to month 6 for uterine volume by TAU/TVU, cm ^{3c}	65.7 (41.3)	46.1 (71.2)	47.8 (60.1)	-109.4 (39.7) ^e	-49.0 (74.1)	-57.0 (61.6)	-48.9 (28.7) ^d	-28.0 (50.6)	-32.0 (42.5)
Mean UFS-QOL score change from baseline to month 6 ^c									
Symptom severity	-15.6 (3.7)	-8.0 (1.8)	-9.1 (1.6)	-53.6 (3.9) ^f	-47.7 (1.8) ^f	-48.8 (1.7) ^f	-47.8 (2.7) ^f	-35.1 (1.3) ^f	-37.0 (1.2) ^f
HRQL total	17.6 (3.8)	7.4 (1.8)	8.9 (1.6)	58.5 (3.8) ^f	45.2 (1.9) ^f	47.3 (1.7) ^f	51.1 (2.7) ^f	37.8 (1.3) ^f	39.9 (1.2) ^f

Statistical comparisons were not made between adenomyosis subsets.

BID = twice daily; HRQL = health-related quality of life; TAU/TVU = transabdominal/transvaginal ultrasound; UFS-QOL = Uterine Fibroid Symptom and Health-Related Quality of Life.

Four women who were randomized and treated before the trial registration date were excluded from this analysis. Statistical significance compared with placebo was indicated by ^d $P < .05$, ^e $P < .01$, and ^f $P < .001$. 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 using 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.

^a Suppression of bleeding was defined as no bleeding during the final month, with or without spotting.

^b Data are presented as n/N (%) where N, the denominator, is the number of women with at least 38 days on study drug before and including day 1 of treatment. Statistical significance compared with placebo was on the basis of the Cochran–Mantel–Haenszel test using study as stratification factor.

^c Data are presented as least-squares mean (standard error of the mean). Statistical significance compared with placebo was determined by pooling the results from an ANCOVA model with treatment and study as the main effects and baseline as a covariate.

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TABLE 3

Treatment-emergent adverse events.	Placebo			Elagolix 300 mg BID			Elagolix 300 mg BID + add-back therapy		
	Women with uterine fibroids and coexisting adenomyosis (N = 34)	Women with uterine fibroids without adenomyosis diagnosis at baseline (N = 161)	Overall pooled study population (N = 195)	Women with coexisting adenomyosis (N = 32)	Excluding women with adenomyosis (N = 167)	Overall pooled study population (N = 199)	Women with uterine fibroids and coexisting adenomyosis (N = 60)	Women with uterine fibroids without adenomyosis diagnosis at baseline (N = 332)	Overall pooled study population (N = 392)
n (%)									
Any adverse event (AE)	26 (76.5)	104 (64.6)	130 (66.7)	26 (81.3)	140 (83.8)	166 (83.4)	39 (65.0)	243 (73.2)	282 (71.9)
Any serious AE	1 (2.9)	5 (3.1)	6 (3.1)	1 (3.1)	6 (3.6)	7 (3.5)	2 (3.3)	8 (2.4)	10 (2.6)
Any severe AE	1 (2.9)	9 (5.6)	10 (5.1)	2 (6.3)	18 (10.8)	20 (10.1)	5 (8.3)	31 (9.3)	36 (9.2)
Any AE leading to study drug discontinuation	3 (8.8)	10 (6.2)	13 (6.7)	2 (6.3)	20 (12.0)	22 (11.1)	5 (8.3)	33 (9.9)	38 (9.7)
Most common AEs ^a									
Hot flush	2 (5.9)	11 (6.8)	13 (6.7)	21 (65.6)	87 (52.1)	108 (54.3)	11 (18.3)	68 (20.5)	79 (20.2)
Nausea	2 (5.9)	17 (10.6)	19 (9.7)	0	11 (6.6)	11 (5.5)	7 (11.7)	30 (9.0)	37 (9.4)
Headache	3 (8.8)	11 (6.8)	14 (7.2)	5 (15.6)	25 (15.0)	30 (15.1)	4 (6.7)	33 (9.9)	37 (9.4)
Night sweats	1 (2.9)	7 (4.3)	8 (4.1)	8 (25.0)	44 (26.3)	52 (26.1)	5 (8.3)	29 (8.7)	34 (8.7)
Fatigue	0	7 (4.3)	7 (3.6)	0	4 (2.4)	4 (2.0)	4 (6.7)	20 (6.0)	24 (6.1)

Note: Four women who were randomized and treated before the trial registration date were excluded from this analysis. Data are presented as n (%) or n.

^a MedDRA preferred terms in descending order for elagolix 300 mg BID plus add-back overall and then for subjects with adenomyosis. AE = adverse event; BID = twice daily.

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add-back (63.6% [95% CI, 50.9, 76.4]) achieved suppression of bleeding at the final month compared with those who received placebo (3.3% [95% CI, 0, 9.8]) ($P < .001$) (Table 2). Similarly, significantly more women in the adenomyosis subset treated with elagolix plus add-back (61.8% [95% CI, 49.0, 74.7]) achieved amenorrhea at the final month compared with those who received placebo (3.3% [95% CI, 0, 9.8]) ($P < .001$) (Table 2).

Uterine Volume

The mean change from baseline to month 6 in uterine volume with elagolix plus add-back therapy (-48.9 cm^3) was significantly greater than that with placebo (65.7 cm^3) for women in the adenomyosis subset ($P < .05$) but not for women without an adenomyosis diagnosis at baseline (Table 2). Although not statistically significant, elagolix with add-back therapy reduced the mean uterine volume (measured by ultrasound) from baseline in the overall pooled study population, whereas the mean uterine volume increased with placebo (Table 2).

Uterine Fibroid Symptom and Health-Related Quality of Life

In the adenomyosis subset, the elagolix with add-back therapy group showed significantly greater improvements in quality of life than did the placebo group on the basis of the mean change from baseline to month 6 in symptom severity and health-related quality of life total scores ($P < .001$), as measured by the 4-week recall version of the UFS-QOL questionnaire (Table 2). These results were consistent with women without an adenomyosis diagnosis at baseline and the overall pooled study population.

Safety

The incidence of adverse events reported by the adenomyosis subset was consistent across the treatment groups and similar to women without an adenomyosis diagnosis at baseline and the overall pooled study population (Table 3). Among the adenomyosis subset, hot flashes, headache, and nausea were the most frequently reported adverse events and were rated mild or moderate in severity by the investigators. In addition, the levels of these most common adverse events were similar to the overall study population.

DISCUSSION

The results from this pooled analysis of 2 identical phase 3 trials, Elaris UF-1 and UF-2, demonstrate that in women with uterine fibroids and coexisting adenomyosis, elagolix with hormonal add-back therapy, compared with placebo, was effective in reducing heavy menstrual bleeding as measured by multiple endpoints. Although not statistically compared, the rate of reduction of heavy menstrual bleeding in women with uterine fibroids and coexisting adenomyosis was numerically similar to women without an adenomyosis diagnosis at baseline and the overall pooled study population. The efficacy of elagolix with add-back therapy in achieving suppression of bleeding and amenorrhea, reducing uterine volume, and

improving fibroid-related symptom severity and quality of life as well as the safety profile were additionally not affected by coexisting adenomyosis.

In UF-1 and UF-2 combined, 16% of women who had uterine fibroids were additionally diagnosed with adenomyosis at baseline, which is consistent with the literature reporting coexisting adenomyosis in a range of 15%–57% of hysterectomy specimens with uterine fibroids (4, 5, 18–20). Women in our studies with uterine fibroids and coexisting adenomyosis had smaller uterine volumes and fibroid (average and largest) volumes than those without an adenomyosis diagnosis at baseline, which is consistent with retrospective studies (1, 2). A previous publication on these elagolix phase 3 trials demonstrated that elagolix with add-back therapy was effective in reducing heavy menstrual bleeding, irrespective of fibroid location, uterine volume, primary fibroid volume, age, body mass index, race, ethnicity, and baseline MBL (21). In parallel, here, we demonstrated that with a reduction in heavy menstrual bleeding, women with uterine fibroids and coexisting adenomyosis treated with elagolix with add-back therapy had a reduction in ultrasound-measured uterine volume from baseline to the final month, as did women without an adenomyosis diagnosis at baseline and the overall pooled study population.

In our studies, women with uterine fibroids and coexisting adenomyosis were significantly more likely to have worse symptom severity and health-related quality of life than women without a coexisting adenomyosis diagnosis at baseline as measured by the UFS-QOL questionnaire. In addition to heavy menstrual bleeding, women with coexisting adenomyosis may experience pelvic pain because of swelling of endometrial islands confined by the myometrium (22, 23). These associated symptoms of bleeding and pain can have a major impact on a woman's quality of life, psychological and social well-being, and overall health. This subset analysis in women with fibroids and coexisting adenomyosis showed that elagolix with add-back therapy resulted in better quality of life than did placebo on the basis of mean improvement from baseline to month 6 in symptom severity and health-related quality of life total scores. In fact, the symptom severity and health-related quality of life scores of the adenomyosis subset after elagolix with add-back treatment were consistent with the UFS-QOL scores validated in healthy women without fibroids (mean [standard deviation]: 22.5 [21.1] and 86.4 [17.7], respectively) (21). In addition, the mean changes in the scores from baseline to month 6 were considered clinically meaningful (21).

Although most of the women in the trials underwent both ultrasound and MRI (87%), some women who opted out of the MRI subset may have had coexisting adenomyosis that was undetected by ultrasound and were, therefore, not included in the adenomyosis subset. In a review of 23 articles, the sensitivity and specificity of MRI for diagnosis of adenomyosis were 77% and 89%, compared with 72% and 81% for transvaginal ultrasound (16). However, transvaginal ultrasound is more user-dependent. We observed discrepancies between the ultrasound and MRI results, with MRI indicating adenomyosis in 83 of the 126 participants when ultrasound did not.

Few large, prospective randomized controlled studies have been published about the effect of medical treatment of heavy menstrual bleeding associated with uterine fibroids with or without adenomyosis. Although these trials focus specifically on subjects with uterine fibroids, to our knowledge, this subset analysis is the largest prospective, randomized, placebo-controlled study that shows evidence of statistically significant improvements in heavy menstrual bleeding and quality of life with medical treatment in women with both uterine fibroids and adenomyosis.

CONCLUSIONS

In conclusion, efficacy and safety of elagolix 300 mg BID with add-back therapy (estradiol 1 mg/norethindrone acetate 0.5 mg QD), when compared with placebo, in reducing heavy menstrual bleeding in women with uterine fibroids and coexisting adenomyosis were similar to those in women without an adenomyosis diagnosis at baseline and the overall pooled study population. These results suggest that elagolix with add-back therapy is effective in reducing heavy menstrual bleeding in women with uterine fibroids despite the presence of coexisting adenomyosis. Future larger studies investigating the effect of elagolix in women with uterine fibroids and coexisting adenomyosis may be warranted.

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Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a research proposal and statistical analysis plan and execution of a Data Sharing Agreement. Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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