HHS Public Access

Author manuscript

*Am J Obstet Gynecol*. Author manuscript; available in PMC 2022 January 29.

Published in final edited form as:

*Am J Obstet Gynecol*. 2021 January ; 224(1): 72.e1–72.e50. doi:10.1016/j.ajog.2020.07.032.

# Predictors of response for elagolix with add-back therapy in women with heavy menstrual bleeding associated with uterine fibroids

**Ayman Al-Hendy, MD, PhD**,
Department of Obstetrics and Gynecology, The University of Illinois College of Medicine, Chicago, IL

**Linda Bradley, MD**,
Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH

**Charlotte D. Owens, MD**,
AbbVie Inc, North Chicago, IL

**Hui Wang, PhD**,
AbbVie Inc, North Chicago, IL

**Kurt T. Barnhart, MD**,
Department of Obstetrics and Gynecology, University of Pennsylvania, Philadelphia, PA

**Eve Feinberg, MD**,
Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL

**William D. Schlaff, MD**,
Department of Obstetrics and Gynecology, Thomas Jefferson University, Philadelphia, PA

**Elizabeth E. Puscheck, MD**,
Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI

**Alice Wang, MA**,
AbbVie Inc, North Chicago, IL

**Veronica Gillispie, MD**,
Department of Obstetrics and Gynecology, Ochsner Baptist Hospital, New Orleans, LA

**Sandra Hurtado, MD**,
Department of Obstetrics and Gynecology, University of Texas Health Center, Houston, TX

**Ozgul Muneyyirci-Delale, MD**,
Department of Obstetrics and Gynecology, SUNY Downstate Health Science University, Brooklyn, NY

**David F. Archer, MD**,
Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA



Corresponding author: Ayman Al-Hendy, MD. aalhendy@uic.edu.

**Bruce R. Carr, MD**,
Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX

**James A. Simon, MD**,
Department of Obstetrics and Gynecology, George Washington University, IntimMedicine Specialists, Washington, DC

**Elizabeth A. Stewart, MD**
Department of Obstetrics and Gynecology, Mayo Clinic and Mayo Clinic Alix School of Medicine, Rochester, MN

## Abstract

**BACKGROUND:** Uterine fibroids are one of the most common neoplasms found among women globally, with a prevalence of approximately 11 million women in the United States alone. The morbidity of this common disease is significant because it is the leading cause of hysterectomy and causes significant functional impairment for women of reproductive age. Factors including age, body mass index, race, ethnicity, menstrual blood loss, fibroid location, and uterine and fibroid volume influence the incidence of fibroids and severity of symptoms. Elagolix is an oral gonadotropin-releasing hormone receptor antagonist that competitively inhibits pituitary gonadotropin-releasing hormone receptor activity and suppresses the release of gonadotropins from the pituitary gland, resulting in dose-dependent suppression of ovarian sex hormones, follicular growth, and ovulation. In Elaris Uterine Fibroids 1 and Uterine Fibroids 2, 2 replicate multicenter, double-blind, randomized, placebo-controlled, phase 3 studies, treatment of premenopausal women with elagolix with hormonal add-back therapy demonstrated reduction in heavy menstrual bleeding associated with uterine fibroids.

**OBJECTIVE:** This analysis aimed to evaluate the safety and efficacy of elagolix (300 mg twice a day) with add-back therapy (1 mg estradiol/0.5 mg norethindrone acetate once a day) in reducing heavy menstrual bleeding associated with uterine fibroids in various subgroups of women over 6 months of treatment.

**STUDY DESIGN:** Data were pooled from Elaris Uterine Fibroid-1 and Uterine Fibroid-2 studies, which evaluated premenopausal women (18–51 years) with heavy menstrual bleeding (>80 mL menstrual blood loss per cycle, alkaline hematin methodology) and ultrasound-confirmed uterine fibroid diagnosis. Subgroups analyzed included age, body mass index, race, ethnicity, baseline menstrual blood loss, fibroid location, and uterine and primary fibroid volume (largest fibroid identified by ultrasound). The primary endpoint was the proportion of women with <80 mL menstrual blood loss during the final month and ≥50% menstrual blood loss reduction from baseline to final month. Secondary and other efficacy endpoints included mean change in menstrual blood loss from baseline to final month, amenorrhea, symptom severity, and health-related quality of life. Adverse events and other safety endpoints were monitored.

**RESULTS:** The overall pooled Elaris Uterine Fibroid-1 and Uterine Fibroid-2 population was typical of women with fibroids, with a mean age of 42.4 (standard deviation, 5.4) years and a mean body mass index of 33.6 (standard deviation, 7.3) $kg/m^2$ and 67.6% of participants being black or African American women. A wide range of baseline uterine and fibroid volumes

and menstrual blood loss were also represented in the overall pooled study population. In all subgroups, the proportion of responders to the primary endpoint, mean change in menstrual blood loss, amenorrhea, reduction in symptom severity, and improvement in health-related quality of life were clinically meaningfully greater for women who received elagolix with add-back therapy than those who received placebo and consistent with the overall pooled study population for the primary endpoint (72.2% vs 9.3%), mean change in menstrual blood loss (−172.5 mL vs −0.8 mL), amenorrhea (50.4% vs 4.5%), symptom severity (−37.1 vs −9.2), and health-related quality of life score (39.9 vs 8.9). Adverse events by subgroup were consistent with the overall pooled study population.

**CONCLUSION:** Elagolix with hormonal add-back therapy was effective in reducing heavy menstrual bleeding associated with uterine fibroids independent of age, body mass index, race, ethnicity, baseline menstrual blood loss, fibroid location, and uterine and primary fibroid volume.

### Keywords

age; BMI; elagolix; fibroid location; fibroid volume; heavy menstrual bleeding; leiomyoma; menstrual blood loss; race; subgroups; uterine fibroid; uterine volume

## Introduction

Uterine fibroids are the most common neoplasms found among women globally, with a prevalence of approximately 11 million women in the United States.[1–3] Uterine fibroids cause significant morbidity in 25% to 50% of affected women.[4] The most common symptoms include heavy menstrual bleeding, which occurs in 46% to 59% of symptomatic women and can lead to anemia and fatigue; reproductive dysfunction; and bulk symptoms including bowel and bladder dysfunction, pelvic pain, and abdominal protrusion.[2,5,6]

Factors including race, ethnicity, fibroid location, uterine and fibroid volume, age, and body mass index (BMI) influence the incidence of fibroids and symptom severity.[7–14] Race and ethnicity are key risk factors for uterine fibroids.[4] African American women have a 3-fold greater incidence and relative risk of uterine fibroids, and disease onset occurs 10 to 15 years earlier than in women of other races.[9] In addition, women of Latino descent have a 1.3-fold increase in risk of uterine fibroids compared with non-Latina women.[10]

Fibroid location and uterine and fibroid volume have been shown to be associated with severity of heavy menstrual bleeding. Submucosal or International Federation of Gynecology and Obstetrics (FIGO) classification system types 0 to 3 fibroids are thought to be the main contributors to heavy menstrual bleeding, with intramural fibroids (FIGO type 4) contributing more than subserosal or cervical ones (FIGO types 5–8).[13–17] Various studies have also shown that even small fibroids can be associated with heavy menstrual bleeding, with an increased risk as fibroid size increases.[14]

Uterine fibroid incidence increases with age until menopause, and symptoms most often resolve after menopause.[7,18] The relationship between BMI and uterine fibroids is mixed, with some studies finding correlations between BMI and uterine weight with fibroids[8] and

others demonstrating that weight gain is positively associated with the risk of fibroids only among women with a history of pregnancy.[19]

In addition to contributing to the risk of uterine fibroids, the aforementioned factors also traditionally influence treatment decisions for the disease.[20,21] Multiple treatment options exist for fibroids, including hysterectomy, myomectomy, myolysis, uterine artery embolization, and medical management. Moreover, most women who seek treatment for symptomatic uterine fibroids prefer an alternative to surgery.[22]

Long-term medical therapy specifically for the treatment of heavy menstrual bleeding associated with uterine fibroids is currently unavailable in the United States. Recently, the efficacy of oral gonadotropin-releasing hormone (GnRH) antagonists in reducing heavy menstrual bleeding associated with uterine fibroids has been studied in clinical trials, with GnRH antagonists being considered as potentially long-term treatment options.[23]

Elagolix is an oral GnRH receptor antagonist that competitively inhibits pituitary GnRH receptor activity and suppresses pituitary release of gonadotropins, resulting in a dose-dependent suppression of ovarian sex hormones, follicular growth, and ovulation, without the initial flare effects seen with GnRH agonists.[24,25] Hormonal add-back therapy coadministered with elagolix attenuates hypoestrogenic effects.[25] In 2 replicate multicenter, double-blind, randomized, placebo-controlled, phase 3 studies, Elaris Uterine Fibroids 1 (UF-1) and Uterine Fibroids 2 (UF-2), elagolix with hormonal add-back therapy demonstrated reduction in heavy menstrual bleeding associated with uterine fibroids over 6 months of treatment, with statistically significant reductions in menstrual blood loss as early as 1 month of treatment.[23] This analysis evaluates the efficacy in reducing heavy menstrual bleeding associated with uterine fibroids and the safety of elagolix with hormonal add-back therapy in subgroups that include age, BMI, race, ethnicity, baseline menstrual blood loss, fibroid location, and uterine and primary fibroid volume.

## Materials and Methods

### Study design

Data were pooled from 2 replicate multicenter, double-blind, randomized, placebo-controlled, phase 3 studies, Elaris UF-1 and UF-2, previously published by Schlaff et al.[23] One patient in UF-1 and 3 patients in UF-2 who underwent randomization were enrolled before the trial registration date on ClinicalTrials.gov because of an administrative error. Premenopausal women aged 18 to 51 years at the time of screening with heavy menstrual bleeding demonstrated by >80 mL of menstrual blood loss per menstrual cycle for at least 2 separate cycles as measured by the alkaline hematin method and pelvic ultrasound (transabdominal or transvaginal)–confirmed uterine fibroid diagnosis were included in the studies. Inclusion and exclusion criteria, as well as patient disposition, were previously reported.[23]

Both clinical trials used a washout period of hormone therapies (if applicable), a screening period of 2.5 to 3.5 months, and a treatment period of 6 months. Women started treatment within 10 days of the start of their menses and were randomly assigned in a 2:1:1 ratio to

elagolix 300 mg twice daily with hormonal add-back therapy (estradiol 1 mg/norethindrone acetate 0.5 mg once daily), elagolix 300 mg twice daily alone, or placebo in a matched, double-blind manner. Elagolix alone was included only as a reference arm to characterize the effect of add-back therapy on the safety or tolerability of elagolix. Therefore, the focus of this subgroup analysis was on elagolix with add-back therapy, as compared with placebo.

The trials were conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines 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 or ethics committee for all other study sites. All women provided written, informed consent.

## Efficacy endpoints and safety assessments

The primary, secondary, and other efficacy endpoints described here assessed the treatment effect of elagolix with hormonal add-back therapy across key variables potentially affecting efficacy. Demographic subgroups analyzed for all key endpoints included age, BMI, race, and ethnicity. Disease severity subgroups based on baseline characteristics included menstrual blood loss, FIGO classification, uterine volume, and primary fibroid volume. Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QOL) scores were analyzed for the following subgroups: age, BMI, race, menstrual blood loss, FIGO classification, uterine volume, and primary fibroid volume. Uterine volume and primary fibroid volume, defined at baseline as the fibroid with the largest volume, were measured by ultrasound. All ultrasound images were read by independent central reviewers (Parexel International Corporation, Waltham, MA). Median values used to define subgroups were based on the overall median of the pooled Elaris UF-1 and UF-2 data set.

At baseline, fibroids were grouped by the following FIGO types for location: 0–3, 4, and 5–8.[13] The analyses were completed for (1) lowest FIGO type, (2) highest FIGO type, and (3) FIGO type for the primary fibroid. These 3 subgroups were identified to account for bleeding contributed by submucosal fibroids (lower FIGO types), subserosal fibroids (higher FIGO types), and primary fibroids. Although patients with fibroids characterized as FIGO 0 were excluded during screening, 13 patients from Elaris UF-1 and UF-2 were classified as FIGO 0 at baseline. These women were allowed to continue in the study as they were eligible at the time of screening.

Clinically meaningful reduction in menstrual blood loss was measured by the primary efficacy endpoint, which was the proportion of women who had both <80 mL of menstrual blood loss during the final month and ≥50% reduction in menstrual blood loss from baseline to final month. The mean change from baseline in menstrual blood loss to final month was a secondary endpoint, and the other efficacy endpoint was the proportion of women who achieved amenorrhea at the final month. 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). All bleeding endpoints were objectively measured using the alkaline hematin method.[26]

Changes from baseline to month 6 in the UFS-QOL questionnaire scores were also analyzed. The 4-week recall version of the UFS-QOL questionnaire includes a symptom severity score and a health-related quality of life (HRQoL) total score that is the sum of 6 subscale scores: concern, activities, energy/mood, control, self-conscious, and sexual function.[27] For symptom severity, scores ranged from 0 to 100, with higher scores indicating increased severity; for HRQoL total and subscales, scores ranged from 0 to 100, with higher scores indicating better quality of life.[28]

Treatment-emergent adverse events were assessed by subgroup and the overall pooled study population.

### Statistical analysis

Within each level of a subgroup, analysis for the primary efficacy endpoint consisted of a logistic regression with the responder as the response variable, baseline menstrual blood loss volume as a covariate, and treatment and study as the main effects. Women who prematurely discontinued the study drug use because of “lack of efficacy,” “requires surgery or invasive intervention for treatment of uterine fibroids,” or adverse events were considered as nonresponders, regardless of whether the 2 conditions were met or not.

Statistical analyses for the secondary and other endpoints and sensitivity analyses of the primary endpoint were previously described.[23] Adverse events were summarized based on MedDRA (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Geneva, Switzerland) version 21.0. The Breslow-Day test was used to examine the homogeneity of treatment effect for each event type overall and only if there were at least 10 subjects per treatment group with an event within each subgroup.

SAS software (version 9.4, SAS Institute, Cary, NC), with a 2-sided significance level of .05 and a confidence interval (CI) of 95%, was used to perform statistical analyses. Missing final month menstrual blood loss data were imputed using multiple imputation.

## Results

A total of 791 women were randomized in the Elaris UF-1 and UF-2 studies, with 790 treated and 617 (78.0%) completing the treatment period. This overall pooled study population was typical of women with uterine fibroids: most women were black or African American (67.6%), the mean age was 42.4 years (SD, 5.4), and the mean BMI was 33.6 $kg/m^2$ (SD, 7.3).[23] Furthermore, most women in the overall pooled study population had multiple fibroids, and broad ranges of baseline menstrual blood loss volume (83.8–1207.1 mL), uterine volume (71.6–3347.9 $cm^3$), and primary fibroid volume (1.0–1081.5 $cm^3$) were represented.[23] No notable differences were observed among the baseline characteristics of the overall pooled study population and all patient demographic and disease severity subgroups (Supplemental Table 1).

### Primary efficacy endpoint

The efficacy of elagolix with add-back hormonal therapy compared with placebo was maintained across all subgroups (Figure 1 and Supplemental Figure 1). The proportion of women in each subgroup who achieved the primary endpoint was considerably greater with elagolix with add-back (range, 59%–80%) than placebo (range, 4%–16%), consistent with the overall pooled study population (placebo, 9%; elagolix with add-back, 72%) (Supplemental Figure 2). The odds ratios (ORs) for elagolix with add-back were numerically higher in women with larger uteri (≥median, 42.8; 95% CI, 16.615–110.318; <median, 17.9; 95% CI, 8.928–36.245) and larger primary fibroids (≥median, 53.8; 95% CI, 18.845–153.793; <median, 16.0; 95% CI, 8.110–31.691) (Figure 1). The results also demonstrated consistent efficacy of elagolix with add-back therapy among all fibroid locations (Supplemental Figure 2).

### Menstrual blood loss

There was a statistically significant reduction in mean menstrual blood loss volume from baseline to final month with elagolix with add-back vs placebo in all subgroups (Table 1 and Supplemental Table 2). The change in mean menstrual blood loss in the elagolix with add-back group ranged from −206.4 mL (standard error [SE], 16.7) to −140.9 mL (SE, 10.6), whereas mean menstrual blood loss in the placebo group ranged from −34.4 mL (SE, 19.1) to 25.7 mL (SE, 25.2). This result was similar to the change in mean menstrual blood loss from baseline to final month with elagolix with add-back (−172.5 mL; SE, 7.6) and placebo (−0.8 mL; SE, 10.8) in the overall pooled study population (Table 1).

### Amenorrhea

The proportion of women in each subgroup who achieved amenorrhea at the final month with elagolix with add-back (range, 44.3%–59.7%) was statistically significantly greater than placebo (range, 0.0%–15.8%) and consistent with the results of the overall pooled study opulation (elagolix with add-back: 50.4%; 95% CI, 45.2–55.6 vs placebo: 4.5%; 95% CI, 1.5–7.6) (Supplemental Table 3). In addition, the ORs for elagolix with add-back were consistent across the subgroups.

### Symptom severity and health-related quality of life

Among all subgroups, the mean change in symptom severity score from baseline to month 6 in the elagolix with add-back treatment group (range, −42.3 to −33.3) was statistically significantly greater than the mean change in the placebo group (range, −14.6 to −1.4) (Figure 2, A, and Supplemental Figure 3, A). Similarly, the mean change in HRQoL total score from baseline to month 6 in the elagolix with add-back treatment group (range, 36.6–43.5) was statistically significantly greater than the mean change in the placebo group (range, 2.4–14.1) among all subgroups (Figure 2, B, and Supplemental Figure 3, B). Similar results were also seen among all subgroups for each of the 6 UFS-QOL subscales (Supplemental Tables 5–10). The UFS-QOL results for each of the subgroups were consistent with the results from the overall pooled study population (Figure 2 and Supplemental Figure 3; Supplemental Tables 4–10).

### Safety

Adverse events were described for each demographic and disease severity subgroup. The percentages of women treated with elagolix with add-back who reported at least 1 adverse event appeared similar among all subgroups, and most adverse events were classified as mild or moderate, consistent with previous results reported in Schlaff et al[23] (Supplemental Tables 11 and 12).

## Structured Discussion or Comment

### Principal findings

This subgroup analysis demonstrated that treatment with elagolix with hormonal add-back therapy is efficacious in reducing heavy menstrual bleeding, achieving amenorrhea, and improving severity of symptoms and HRQoL in women across all ages and BMIs, various race and ethnicity groups, and over a wide range of baseline menstrual blood loss volume and uterine anatomy parameters.

### Clinical implications

These study results show that response to elagolix with add-back therapy is not diminished by clinical or uterine factors that indicate more severe disease. Thus, all women may benefit from medical therapy before resorting to surgery.

Hysterectomy is the long-standing primary management option for symptomatic fibroids; however, it is not without a loss of fertility and surgical complications.[22] In addition, hysterectomy, even with conservation of both ovaries, has also been linked to long-term cardiovascular risks.[29] Despite the risks associated with hysterectomy, many women are not offered alternatives to hysterectomy for the treatment of heavy menstrual bleeding associated with uterine fibroids.[30]

Current medical management options used for symptomatic uterine fibroids include nonhormonal treatments such as nonsteroidal antiinflammatory drugs and antifibrinolytics and hormonal options, such as combination oral contraceptives, levonorgestrel-releasing intrauterine systems, progestogens, and GnRH agonists. In Canada and Europe, ulipristal acetate is also available; however, although effective, it is indicated for only 1 treatment course unless the patient is not a surgical candidate. Treatment breaks and monitoring are also required.[21,31] Current options for medical treatment of symptomatic fibroids have been shown to produce inconsistent results across subsets of women. Furthermore, such options are only approved in the United States for short-term presurgical treatment of women who experience anemia associated with fibroid-related heavy menstrual bleeding.

Further adding to the challenge of medical management of heavy menstrual bleeding associated with uterine fibroids is a paucity of literature on the medical management of different subgroups of women with uterine fibroids and a lack of randomized trials comparing various treatment options.[32] A recent report from the Agency for Healthcare Research and Quality guidance on fibroid management showed that there is little evidence for individualized management.[33] This subgroup analysis aims to close this gap.

Historically, factors such as uterine and fibroid volume, fibroid location, and age have been used to exclude women from medical therapy. Data from this study support the contention that all women should be offered a medical trial for the treatment of heavy menstrual bleeding associated with fibroids to allow women to choose from all available, effective treatment options.[32] This study provides information in an area with limited data and demonstrated that regardless of patient demographics and disease phenotype, elagolix with add-back therapy was effective at reducing heavy menstrual bleeding.

Treatment with elagolix with add-back therapy also demonstrated significantly decreased symptom severity and improved HRQoL in all subgroups of women. Treatment with elagolix with add-back resulted in UFS-QOL scores similar to those of women without uterine fibroids (symptom severity, 22.5; SD, 21.1; HRQoL total score, 86.4; SD, 17.7).[28] Moreover, changes of 9 to 15 points in UFS-QOL are considered to be clinically meaningful, a target achieved across subgroups in this study (Figure 2 and Supplemental Figure 3; Supplemental Tables 4–10).

## Research implications

It has been hypothesized that submucosal fibroids contribute to heavy menstrual bleeding; by extension, the further away the fibroid is from the endometrial cavity, the less likely it will be to contribute to bleeding. However, studies have demonstrated that regardless of location, fibroids are biologically active tissues that produce vasoactive and other regulatory factors that can alter the endometrium in a paracrine manner.[34–36] The consistent baseline mean menstrual blood loss (Supplemental Table 1) and efficacy of elagolix with add-back therapy across all fibroid locations by FIGO classification (Figure 1 and Supplemental Figure 2), which demonstrate reduction of heavy menstrual bleeding independent of location in this study, may support the paracrine effect of fibroids.

## Strengths and limitations

Women who are at the highest risk for fibroids or who exhibit the most severe symptoms and thus are most likely to be encountered in everyday clinical practice were represented in this study. Although the study was limited by smaller sample sizes for a few of the subgroups, considerable or statistically significant results were still achieved for key endpoints.

## Conclusions

Elagolix with hormonal add-back therapy, an oral medical therapy for the treatment of heavy menstrual bleeding associated with uterine fibroids, appears effective across all patient demographics and disease phenotypes and shows a trend to work better with more extensive disease. This broad efficacy opens the door for new ways of thinking regarding patient selection for longer term medical management of women with heavy menstrual bleeding associated with fibroids who previously may not have been offered medical management, only surgical intervention.

## Data Sharing

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 (eg, 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 following 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

AbbVie and the authors thank the women who participated in these clinical trials and all the study investigators and vendors for their contributions. They would also like to acknowledge Ronald D. Luff, MD, MPH, Director of Anatomic Pathology for Clinical Trials; his associates; and dedicated staff at Quest Diagnostics for providing all the anatomical pathology safety testing for Elaris UF-1 and UF-2. Erin C. Franceschini, MS, and Jeanie K. Meckes, PhD, employees of AbbVie, Inc, provided medical writing support for this manuscript. AbbVie provided funding for these activities.

A.A.-H. has provided consulting services to AbbVie, Allergan, Bayer, Myovant, and MD Stem Cells, and he is grant funded by the National Institutes of Health for fibroid-related research (R01 ES 028615–01, R01 HD 087417, R01 HD 094378, and R01 HD 094380). In addition, he holds a patent for Methods for novel diagnostics and therapeutics for uterine sarcoma (US Patent No. 9,790,562 B2). L.B. has served as a scientific advisor for AbbVie, Bayer, Allergan, Boston Scientific, Medtronics, and Karl Storz and has received research support from Bayer and royalties from UpToDate, Elsevier, and Wolters Kluwer. C.D.O. is an AbbVie employee and holds stock or stock options. H.W. is an AbbVie employee and holds stock or stock options. K.T.B. has served as a consultant to AbbVie and Bayer and served on the AbbVie Data and Safety Monitoring Committee. E.F. has served as a consultant to AbbVie, Natera, and CooperSurgical and served on the AbbVie Data and Safety Monitoring Committee. W.D.S. has served as a consultant to AbbVie and has received research support from AbbVie. E.E.P. has received research funding from AbbVie, Bayer, Ferring, and ObsEva and served on the Clinical Events Committee for Femasys. A.W. is an AbbVie employee and holds stock or stock options. V.G. has served as a study investigator for AbbVie and has served as a consultant to AbbVie. S.H. has served as a consultant for AbbVie; served on the speaker's bureau for AbbVie, Merck, and Bayer; and served as an investigator for AbbVie, Allergan, Amgen, Bayer, Femasys, Ferring, Myovant, ObsEva, and TherapeuticsMD. O.M.-D. is a study investigator for AbbVie, Bayer, ObsEva, and Ferring. D.F.A. has received research support from AbbVie, TherapeuticsMD, Bayer HealthCare, Endoceutics, Glenmark, Shionogi, Symbio, and Radius and compensation from AbbVie, TherapeuticsMD, Bayer HealthCare, Endoceutics, Agile Pharmaceuticals, Exeltis/CHEMO France, and TEVA/HR Pharma for consulting. B.R.C. has received research support from AbbVie and Syneract, Inc (M360-L102) and served on the Repros Therapeutics Data and Safety Monitoring Board. J.A.S. has served or is currently serving as a consultant to or on the advisory boards of AbbVie, Inc; Allergan, Plc; AMAG Pharmaceuticals, Inc; Amgen; Ascend Therapeutics; Bayer HealthCare Pharmaceuticals, Inc; CEEK Enterprises, LLC; Covance, Inc; Daré Bioscience; Duchesnay USA; Hologic, Inc; KaNDy/NeRRe Therapeutics, Ltd; Mitsubishi Tanabe Pharma Development America, Inc; ObsEva SA; Palatin Technologies; Sanofi S.A.; Shionogi, Inc; Sprout, Inc; and TherapeuticsMD. He has also served or is currently serving on the speaker's bureau for AbbVie, Inc; AMAG Pharmaceuticals, Inc; Duchesnay USA; Novo Nordisk; Shionogi, Inc; and TherapeuticsMD. He has received or is currently receiving grant/research support from AbbVie, Inc; Allergan, Plc; Agile Therapeutics; Bayer Healthcare, LLC; Endoceutics, Inc; GTx, Inc; Ipsen;

Myovant Sciences; New England Research Institute, Inc; ObsEva SA; Palatin Technologies; Symbio Research, Inc; TherapeuticsMD; and Viveve Medical. He is a stockholder in Sermonix Pharmaceuticals. E.A.S. has been a consultant for AbbVie, Bayer, ObsEva, and Myovant. She has received research support from the National Institutes of Health related to uterine fibroids (R01HD 60503 and P50HS023418) and holds a patent for Methods and Compounds for Treatment of Abnormal Uterine Bleeding (US 6440445), which has no commercial activity. She has received royalties from UpToDate and payments for the development of educational content from the Med Learning Group and Peer View.

AbbVie Inc funded this study and participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication. The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or nonfinancial, relating to this research and its publication have been disclosed. No honoraria or payments were made for authorship.

The Elaris UF-1 study was registered with the U.S. National Library of Medicine at www.ClinicalTrials.gov (NCT02654054) on January 8, 2016; the initial participant enrollment date was December 22, 2015. The Elaris UF-2 study was registered with the U.S. National Library of Medicine at www.ClinicalTrials.gov (NCT02691494) on February 22, 2016; the initial participant enrollment date was February 3, 2016.

Parts of these study results have previously been presented at the 75th American Society of Reproductive Medicine 2019 Scientific Congress & Expo, Philadelphia, PA, October 12e16, 2019, and at the AAGL 2019 Global Congress on Minimally Invasive Gynecologic Surgery, Vancouver, Canada, November 9e13, 2019. They were also presented virtually at the 2020 69th American College of Obstetrics & Gynecology Annual Clinical and Scientific Meeting, Seattle, WA, October 30–31, 2020.

## References

1. Bulun SE. Uterine fibroids. N Engl J Med 2013;369:1344–55. [PubMed: 24088094]
2. Fuldeore MJ, Soliman AM. Patient-reported prevalence and symptomatic burden of uterine fibroids among women in the United States: findings from a cross-sectional survey analysis. Int J Womens Health 2017;9:403–11. [PubMed: 28652819]
3. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, prevalence, and treatment of uterine fibroids: a survey of U.S. women. J Womens Health (Larchmt) 2018;27: 1359–67. [PubMed: 30230950]
4. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. Nat Rev Dis Primers 2016;2:16043. [PubMed: 27335259]
5. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7. [PubMed: 12548202]
6. Hapangama DK, Bulmer JN. Pathophysiology of heavy menstrual bleeding. Womens Health (Lond) 2016;12:3–13. [PubMed: 26695831]
7. Marshall LM, Spiegelman D, Barbieri RL, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997;90:967–73. [PubMed: 9397113]
8. Dandolu V, Singh R, Lidicker J, Harmanli O. BMI and uterine size: is there any relationship? Int J Gynecol Pathol 2010;29:568–71. [PubMed: 20881854]
9. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med 2010;28:204–17. [PubMed: 20414843]
10. Wilcox LS, Koonin LM, Pokras R, Strauss LT, Xia Z, Peterson HB. Hysterectomy in the United States, 1988e1990. Obstet Gynecol 1994;83:549–55. [PubMed: 8134065]
11. Marshall LM, Spiegelman D, Goldman MB, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 1998;70: 432–9. [PubMed: 9757871]

12. Wise LA, Palmer JR, Harlow BL, et al. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol 2004;159:113–23. [PubMed: 14718211]
13. Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. Fertil Steril 2011;95:2204–8. 2208.e1–3. [PubMed: 21496802]
14. Wegienka G, Baird DD, Hertz-Picciotto I, et al. Self-reported heavy bleeding associated with uterine leiomyomata. Obstet Gynecol 2003;101:431–7. [PubMed: 12636944]
15. Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet 2018;143:393–408. [PubMed: 30198563]
16. Buttram VC Jr, Reiter RC. Uterine leiomyomata: etiology, symptomatology, and management. Fertil Steril 1981;36:433–45. [PubMed: 7026295]
17. Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol 1999;94:516–20. [PubMed: 10511351]
18. Stewart EA. Clinical practice. Uterine fibroids. N Engl J Med 2015;372:1646–55. [PubMed: 25901428]
19. Wise LA, Palmer JR, Spiegelman D, et al. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology 2005;16:346–54. [PubMed: 15824551]
20. Simon JA, Catherino W, Segars JH, et al. Ulipristal acetate for treatment of symptomatic uterine leiomyomas: a randomized controlled trial. Obstet Gynecol 2018;131:431–9. [PubMed: 29420395]
21. Donnez J, Tatarchuk TF, Bouchard P, et al. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409–20. [PubMed: 22296075]
22. Borah BJ, Nicholson WK, Bradley L, Stewart EA. The impact of uterine leiomyomas: a national survey of affected women. Am J Obstet Gynecol 2013;209:319.e1–20. [PubMed: 23891629]
23. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. N Engl J Med 2020;382: 328–40. [PubMed: 31971678]
24. 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. [PubMed: 23885105]
25. 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. [PubMed: 28323948]
26. Magnay JL, Nevatte TM, Dhingra V, O'Brien S. Menstrual blood loss measurement: validation of the alkaline hematin technique for feminine hygiene products containing super-absorbent polymers. Fertil Steril 2010;94: 2742–6. [PubMed: 20447631]
27. Coyne KS, Soliman AM, Margolis MK, Thompson CL, Chwalisz K. Validation of the 4 week recall version of the Uterine Fibroid Symptom and Health-related Quality of Life (UFS-QOL) Questionnaire. Curr Med Res Opin 2017;33:193–200. [PubMed: 27733082]
28. Spies JB, Coyne K, Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. Obstet Gynecol 2002;99: 290–300. [PubMed: 11814511]
29. Nicholson WK, Wegienka G, Zhang S, et al. Short-term health-related quality of life after hysterectomy compared with myomectomy for symptomatic leiomyomas. Obstet Gynecol 2019;134:261–9. [PubMed: 31306318]
30. Corona LE, Swenson CW, Sheetz KH, et al. Use of other treatments before hysterectomy for benign conditions in a statewide hospital collaborative. Am J Obstet Gynecol 2015;212: 304.e1–7. [PubMed: 25542564]
31. Raine J. Esmya (ulipristal acetate) for symptoms of uterine fibroids: restrictions to use and requirement to check liver function before, during and after treatment Medicines

and Healthcare products Regulatory Agency. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/safety-alerts/esmyaaug2018update.pdf. Accessed August 18, 2020.

32. Laughlin SK, Stewart EA. Uterine leiomyomas: individualizing the approach to a heterogeneous condition. Obstet Gynecol 2011;117: 396–403. [PubMed: 21252757]
33. Hartmann KE, Fonnesbeck C, Surawicz T, et al. Comparative Effectiveness Review No. 195: management of uterine fibroids Agency for Healthcare Research and Quality. Available at: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cer-195-uterine-fibroids-final-revision.pdf. Accessed August 18, 2020.
34. Stewart EA, Nowak RA. Leiomyoma-related bleeding: a classic hypothesis updated for the molecular era. Hum Reprod Update 1996;2: 295–306. [PubMed: 9080227]
35. Ciarmela P, Islam MS, Reis FM, et al. Growth factors and myometrium: biological effects in uterine fibroid and possible clinical implications. Hum Reprod Update 2011;17:772–90. [PubMed: 21788281]
36. Rackow BW, Taylor HS. Submucosal uterine leiomyomas have a global effect on molecular determinants of endometrial receptivity. Fertil Steril 2010;93:2027–34. [PubMed: 18555231]

## AJOG at a Glance

**Why was this study conducted?**

This study was conducted to evaluate the safety and efficacy of elagolix with hormonal add-back therapy in reducing heavy menstrual bleeding associated with uterine fibroids in subgroups of women of varying ages; body mass indices; races and ethnicities; and baseline menstrual blood loss, fibroid location, and uterine and fibroid volume.

**Key findings**

Elagolix with add-back therapy was safe and effective in reducing heavy menstrual bleeding associated with uterine fibroids in various subgroups of women, similar to the overall pooled study population.

**What does this add to what is known?**

This study demonstrates that elagolix with add-back therapy is both safe and effective over a wide range of clinical variables that characterize women with uterine fibroids and suggests that medical management of women with heavy menstrual bleeding associated with uterine fibroids should be considered for women who previously may have only been considered for surgical management.

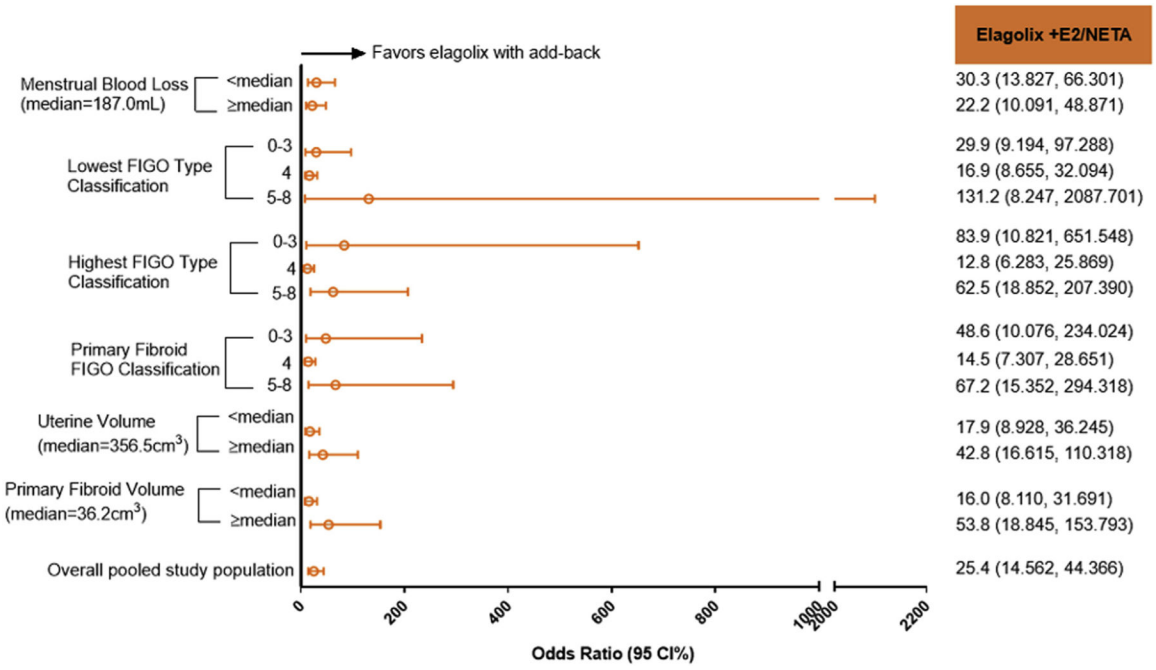


**FIGURE 1. Odds ratios for primary endpoint by factors contributing to disease severity**

The odds ratios with 95% CIs are shown graphically and listed in the table to the right for each disease severity subgroup treated with elagolix with add-back. Odds ratios were determined by pooling the results from a logistic regression model including treatment and study as the main effects and baseline menstrual blood loss volume as a covariate in each data set from multiple imputation under each subgroup level. Median values for uterine and primary fibroid volumes were based on the overall median of the pooled Elaris Uterine Fibroids 1 and Uterine Fibroids 2 data set.

*CI*, confidence interval; *E2*, estradiol; *FIGO*, International Federation of Gynecology and Obstetrics; *NETA*, norethindrone acetate.

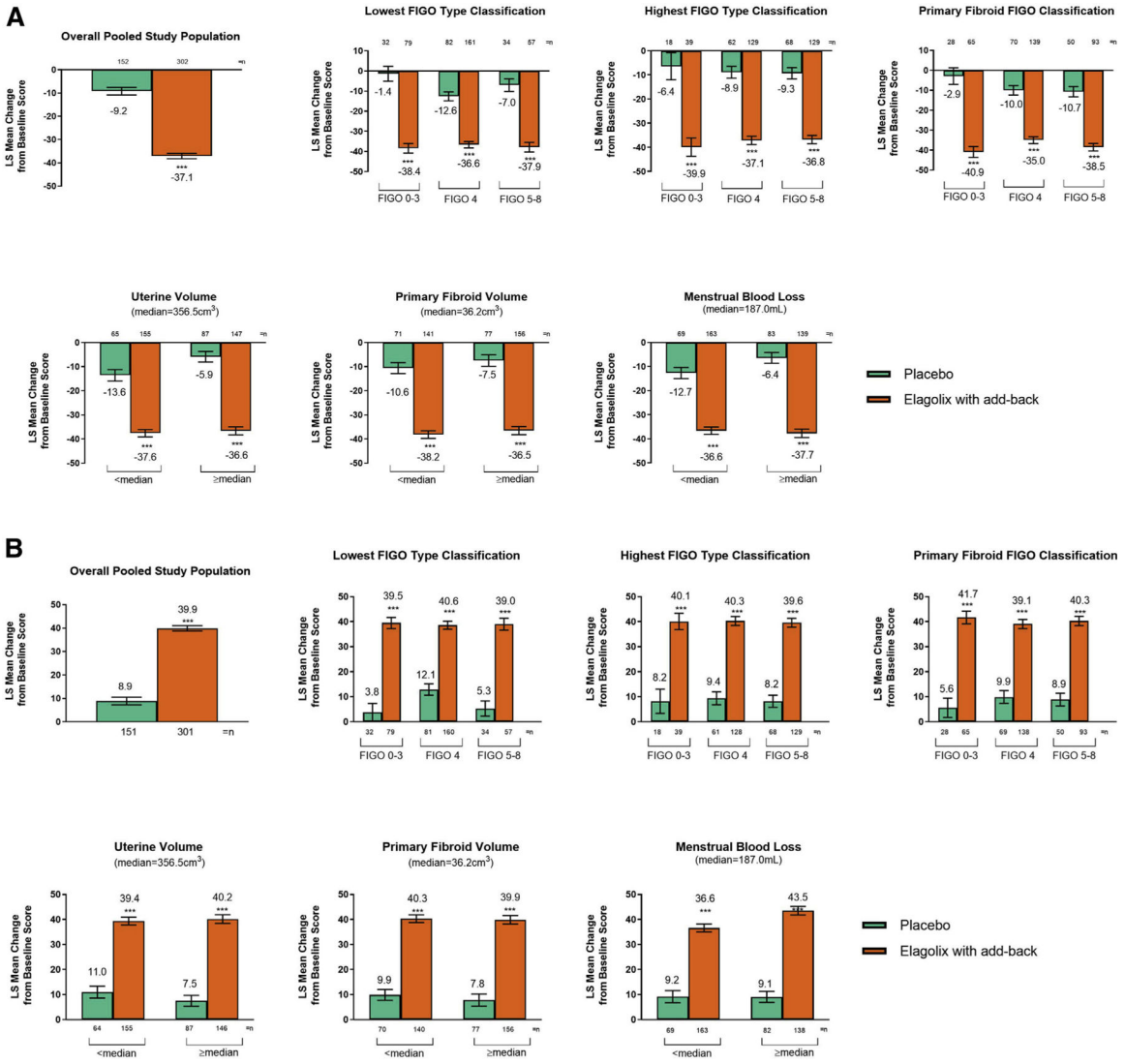


**FIGURE 2. Mean changes in UFS-QOL scores from baseline to month 6 for disease severity subgroups**

**A**, The mean change in symptom severity score for each subgroup is depicted. **B**, The mean change in total HRQoL score for each subgroup is depicted. For symptom severity, a higher score indicates worse symptom severity. For HRQoL, a higher score indicates better quality of life. Data are presented as LS means, with error bars representing the standard error of mean. The change from baseline to month 6 in each parameter was analyzed using an analysis of covariance model with treatment as the main effect and baseline value as a covariate. Median values for uterine and primary fibroid volumes were based on the overall median of the pooled Elaris Uterine Fibroids 1 and Uterine Fibroids 2 data set. The asterisk symbol (***) indicates $P<.001$.

*FIGO*, International Federation of Gynecology and Obstetrics; *HRQoL*, health-related quality of life; *LS*, least-squares; *UFS-QOL*, Uterine Fibroid Symptom and Health-Related Quality of Life.

**TABLE 1**

Change in MBL from baseline to final month by disease severity subgroup

| Factors | Subgroup/treatment | N | Change from baseline in MBL volume to final month, mL (SE) | Difference from placebo, mL (SE) | *P* value |
|---|---|---|---|---|---|
| Overall pooled study population | Placebo | 196 | −0.8 (10.8) | — | — |
| | Elagoli+E2/NETA | 395 | −172.5 (7.6) | −171.7 (13.1) | <.001 |
| Lowest FIGO type classification | 0–3 | | | | |
| | Placebo | 45 | −5.9 (25.0) | | |
| | Elagolix+E2/NETA | 95 | −206.4 (16.8) | −200.5 (30.2) | <.001 |
| | 4 | | | | |
| | Placebo | 110 | 11.8 (14.5) | | |
| | Elagolix+E2/NETA | 225 | −163.3 (10.2) | −175.2 (17.7) | <.001 |
| | 5–8 | | | | |
| | Placebo | 37 | −32.8 (20.3) | | |
| | Elagolix+E2/NETA | 69 | −158.2 (14.7) | −125.4 (25.3) | <.001 |
| Highest FIGO type classification | 0–3 | | | | |
| | Placebo | 25 | −0.7 (26.9) | | |
| | Elagolix+E2/NETA | 47 | −191.6 (18.2) | −190.9 (32.7) | <.001 |
| | 4 | | | | |
| | Placebo | 85 | 0.3 (16.1) | | |
| | Elagolix+E2/NETA | 177 | −177.0 (11.4) | −177.3 (19.8) | <.001 |
| | 5–8 | | | | |
| | Placebo | 82 | −4.7 (17.3) | | |
| | Elagolix+E2/NETA | 165 | −162.5 (12.1) | −157.8 (21.2) | <.001 |
| Primary fibroid FIGO classification | 0–3 | | | | |
| | Placebo | 38 | −7.0 (22.3) | | |
| | Elagolix+E2/NETA | 78 | −216.5 (15.0) | −209.5 (26.9) | <.001 |
| | 4 | | | | |
| | Placebo | 96 | 5.8 (16.3) | | |
| | Elagolix+E2/NETA | 191 | −173.9 (11.8) | −179.7 (20.1) | <.001 |
| | 5–8 | | | | |

| Factors | Subgroup/treatment | N | Change from baseline in MBL volume to final month, mL (SE) | Difference from placebo, mL (SE) | *P* value |
|---|---|---|---|---|---|
| | Placebo | 58 | −16.2 (18.2) | | |
| | Elagolix+E2/NETA | 120 | −142.8 (12.6) | −126.6 (22.3) | <.001 |
| Uterine volume (median=356.5 $cm^3$) | <Median | | | | |
| | Placebo | 88 | −1.3 (15.7) | | |
| | Elagolix+E2/NETA | 203 | −142.8 (10.3) | −141.5 (18.6) | <.001 |
| | ≥Median | | | | |
| | Placebo | 108 | −3.1 (14.5) | | |
| | Elagolix+E2/NETA | 192 | −203.2 (10.9) | −200.1 (18.2) | <.001 |
| Primary fibroid volume (median=36.2 $cm^3$) | <Median | | | | |
| | Placebo | 92 | −23.0 (15.2) | | |
| | Elagolix+E2/NETA | 189 | −140.9 (10.6) | −117.9 (18.4) | <.001 |
| | ≥Median | | | | |
| | Placebo | 100 | 19.3 (15.2) | | |
| | Elagolix+E2/NETA | 200 | −202.2 (10.7) | −221.6 (18.7) | <.001 |

Data are least-squares mean (SE).

Median values for uterine and primary fibroid volumes were based on the overall median of the pooled Elaris UF-1 and UF-2 data set.

Final month was defined as the last 28 days before and including the reference day.

Missing final month MBL was imputed using multiple imputation (subset of the data sets obtained by multiple imputation for the primary analysis for subjects with baseline disease severity).

Statistical significance was determined for the difference between the elagolix with add-back dose group and placebo 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.

*E2*, estradiol; *FIGO*, International Federation of Gynecology and Obstetrics; *MBL*, menstrual blood loss; *NETA*, norethindrone acetate; *SE*, standard error; *UF-1*, Uterine Fibroids 1; *UF-2*, Uterine Fibroids 2.