Elagolix for the management of heavy menstrual bleeding associated with uterine fibroids: results from a phase 2a proof-of-concept study

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Objective: To evaluate the safety and efficacy of elagolix vs. placebo and elagolix with low-dose E_2/progestogen add-back therapy.
Design: Proof-of-concept, dose-ranging, multiple-cohort study.
Setting: Clinics.
Patient(s): Premenopausal women with fibroids and heavy menstrual bleeding (menstrual blood loss [MBL] >80 mL per cycle).
Intervention(s): Three months' treatment with elagolix alone: 100 mg twice daily (BID), 200 mg BID, 300 mg BID, 400 mg once daily (QD), or 600 mg QD (all but the 600 mg QD arm were placebo controlled); or elagolix plus add-back therapy: 200 mg BID plus continuous low-dose E_2 0.5 mg/norethindrone acetate 0.1 mg or elagolix 300 mg BID plus E_2 1 mg continuously and cyclical P 200 mg.
Main Outcome Measure(s): Least-squares mean percentage change in MBL; adverse events (AEs).
Result(s): Mean age was 41.8 years; 73.8% were black; mean baseline MBL was 267 mL. Of randomized women (elagolix alone, n = 160; placebo, n = 50; elagolix with add-back therapy, n = 61), 228 of 271 completed the 3-month treatment period. The MBL percentage change from baseline to last 28 days was significantly greater with elagolix alone (range, −72% to −98%; dose-dependent reduction was highest with 300 mg BID) vs. placebo (range, −8% to −41%); mean percentage changes with add-back regimens were −80% to −85%. Overall AEs were dose independent (elagolix alone, 70.0%–81.3%) but lower with placebo (56.0%) and add-back regimens (55.6%–70.6%). Hot flush was the most common AE (elagolix alone, 45.5%–62.5%; placebo, 12.0%; add-back regimens, 18.5%–26.5%).
Conclusion(s): Elagolix significantly reduced heavy menstrual bleeding in women with fibroids. Low-dose add-back regimens substantially reduced flushing.
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Key Words: Gonadotropin-releasing hormone antagonist, heavy menstrual bleeding, leiomyoma, nonpeptide, oral

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Fibroids (leiomyomas) are the most frequent noncancerous uterine tumors in premenopausal women, with a lifetime incidence reaching approximately 70% and 80% in white and black women, respectively (1). Although the etiology is not fully understood, both estrogen (E) and P play pivotal roles in fibroid growth and symptoms (2).

Among symptomatic women, heavy menstrual bleeding (HMB), often associated with iron-deficiency anemia, is the most frequent symptom of fibroids and the primary reason for hysterectomy in the United States (3, 4). Approximately 200,000 hysterectomies for fibroids

were performed in 2010 in the United States (5), and the direct and indirect costs of fibroids impose a substantial burden, estimated at $5.89–$34.37 billion annually in 2010 (6, 7).

A GnRH agonist may be used as short-term therapy to improve hematologic parameters preoperatively in patients with anemia due to uterine fibroids (8, 9), but there is no approved long-term medical treatment for HMB associated with fibroids in the United States; off-label treatments include oral contraceptives, progestins, levonorgestrel-containing intrauterine device, and tranexamic acid (4, 10). Selective P receptor modulators, including mifepristone, asoprisnil, and ulipristal acetate, showed high efficacy in controlling bleeding in women with uterine fibroids (11–13), and ulipristal acetate was recently approved for the management of symptomatic fibroids in the European Union, on the basis of short-term studies before surgery (14, 15) and long-term treatment when given intermittently to allow intervening resolution of associated endometrial changes (16).

Elagolix is an oral, nonpeptide GnRH antagonist that suppresses the pituitary–ovarian axis in a dose-dependent manner, with partial suppression at lower doses and nearly full suppression at higher doses in previous phase 1 (17) and phase 2 research (18). Phase 2 studies in women with endometriosis-associated pain demonstrated the efficacy of elagolix in reducing pain symptoms, with an acceptable safety and tolerability profile (19–22). Elagolix is also in development for the management of HMB associated with fibroids. The primary objectives of this proof-of-concept, dose-ranging study were to evaluate [1] the safety and efficacy of elagolix (total daily doses [TDDs] of 200–600 mg) vs. placebo to reduce HMB in premenopausal women with HMB and fibroids and [2] the effects of 2 low-dose E_2/progestogen add-back therapy regimens on efficacy, safety, and tolerability when used with elagolix. Heavy menstrual bleeding, generally greater than average values in menstruating women (23), was defined in this study as menstrual blood loss (MBL) >80 mL per cycle, which is commonly accepted (24) and used in clinical research (25). The overall goal of this 3-month study was to select the most appropriate dose(s) of elagolix for future phase 2b/3 studies of longer duration. To our knowledge this is the first study that evaluated the impact of E_2/progestogen-based add-back therapy on the efficacy and safety of a GnRH analog (agonist or antagonist) in women with HMB and fibroids.

MATERIALS AND METHODS

Study Population and Key Entry Criteria

The study included premenopausal women aged 20–49 years with a regular menstrual cycle interval of 24–35 days who had HMB (>80 mL per cycle during two to three screening cycles), as assessed by the validated alkaline hematin method (26). The presence of fibroids in eligible women was documented by pelvic ultrasound and confirmed by a central reader, with one fibroid or more with a diameter ≥2 cm, or multiple small fibroids with calculated uterine volume of ≥200 cm^3 to ≤2,500 cm^3. Women were ineligible for the study if they had ultrasound evidence of focal intracavitary lesions (e.g., intracavitary pedunculated fibroid, endometrial polyps), uterine size >2,500 cm^3, abnormal results on endometrial biopsy, or another clinically significant gynecologic disorder. Furthermore, they could not have had myomectomy, uterine artery embolization, or high-intensity focused ultrasound for fibroid destruction within 1 year of study initiation or endometrial ablation at any time. Women were excluded if they had a history of osteoporosis or other metabolic bone disease. Hormonal treatments such as oral contraceptives, GnRH agonists, and progestins were not allowed during treatment, and predefined washout periods for these treatments were required before entering the screening period.

Study Design and Treatments

This phase 2a cohort, proof-of-concept, dose-ranging study (NCT01441635 at https://clinicaltrials.gov/) consisted of a 2.5- to 3.5-month screening period, a 3-month treatment period, and a 3-month follow-up period. Study participants received a TDD of elagolix of 200 mg, 400 mg, or 600 mg. Seven elagolix dosing regimens were evaluated, the first four of which were placebo-controlled and two of which utilized add-back (Supplemental Fig. 1, available online): [1] 100 mg twice daily (BID), [2] 200 mg BID, [3] 300 mg BID, [4] 400 mg once daily (QD), [5] 600 mg QD, [6] 200 mg BID plus continuous low-dose E_2 0.5 mg/norethindrone acetate 0.1 mg (low-dose E_2/NETA [Activella; Novo Nordisk]), and [7] 300 mg BID plus E_2 1 mg continuously and cyclical P 200 mg (cyclical EP [Prometrium; Virtus Pharmaceuticals]) for 12 days of each month. The elagolix 100 mg BID and 400 mg QD doses constituted a single placebo-controlled cohort, added by an adaptive protocol amendment after results from the 200 mg BID and 300 mg BID doses were available, to explore a minimally efficacious dose and a lower-frequency administration schedule. Women with anemia were requested to use iron supplementation during the study.

The study was approved by an institutional review board at each site and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all local and federal laws and regulatory requirements. Participants provided written, informed consent before any study-related procedures.

Endpoints and Assessments

Key efficacy endpoints included mean and percentage change in MBL from baseline to last complete treatment cycle (last 28 days), percentage of women with reduction in MBL to <80 mL and ≥50% from baseline (composite endpoint of response to treatment), percentage of bleeding days, percentage of women with suppression of bleeding and amenorrhea, posttreatment return to menses, and changes in hemoglobin concentrations. Other endpoints included change from baseline in the volume of the largest fibroid and the uterus (both assessed using ultrasound evaluation) and change from baseline in Uterine Fibroid Symptom Quality of Life (UFS-QoL) questionnaire scores (27). This instrument was modified by shortening the recall period from 3 months to 4 weeks and subsequently evaluated for validity using the current trial data (28).

TABLE 1

Study population disposition, demographics, and baseline clinical characteristics.

	PBO-controlled							Not PBO-controlled		
Characteristic	**E300 BID (n = 30)**	**PBO BID (n = 16)**	**E200 BID (n = 35)**	**PBO BID (n = 18)**	**E400 QD (n = 32)**	**E100 BID (n = 33)**	**PBO BID (n = 16)**	**E600 QD (n = 30)**	**E200 BID + E2/NETA (n = 34)**	**E300 BID + CEP (n = 27)**
Randomized or assigned, n	30	16	35	18	32	33	16	30	34	27
Discontinued, n (%)	4 (13.3)	2 (12.5)	7 (20.0)	2 (11.1)	6 (18.8)	6 (18.2)	3 (18.8)	6 (20.0)	5 (14.7)	2 (7.4)
Age (y)										
Mean (SD)	42.6 (5.6)	41.6 (7.1)	43.1 (4.3)	44.0 (4.2)	40.8 (5.5)	42.1 (5.1)	41.1 (5.9)	40.8 (5.8)	40.9 (6.0)	41.6 (5.3)
Range	32–53	26–51	34–52	35–50	29–48	31–49	30–49	26–49	28–50	28–50
Race, n (%)										
Black	23 (76.7)	9 (56.3)	28 (80.0)	14 (77.8)	25 (78.1)	23 (69.7)	13 (81.3)	24 (80.0)	26 (76.5)	15 (55.6)
White	6 (20.0)	6 (37.5)	7 (20.0)	3 (16.7)	5 (15.6)	10 (30.3)	3 (18.8)	5 (16.7)	7 (20.6)	11 (40.7)
BMI (kg/m^2), mean (SD)	29.0 (4.6)	28.3 (4.5)	29.4 (5.6)	29.9 (5.1)	31.7 (5.8)	30.4 (5.5)	31.4 (5.3)	31.1 (4.8)	31.8 (5.2)	29.6 (5.0)
MBL (mL), mean (SD)	206 (125)	334 (414)	334 (316)	252 (160)	210 (109)	271 (160)	434 (550)	216 (122)	245 (176)	266 (207)
Hemoglobin level (g/dL), mean (SD)	11.3 (1.5)	11.0 (1.5)	10.8 (1.6)	10.4 (1.7)	10.9 (1.4)	10.2 (1.6)	10.4 (1.5)	10.8 (1.8)	10.8 (1.3)	10.3 (2.0)
Volume of uterus (cm^3), mean (SD)	576 (371)	490 (459)	685 (513)	523 (515)	416 (234)	473 (397)	432 (273)	496 (359)	529 (326)	659 (343)
Volume of largest fibroid (cm^3), mean (SD)	83 (103)	103 (149)	138 (292)	147 (402)	47 (59)	61 (82)	46 (52)	87 (121)	66 (64)	149 (171)
Location of largest fibroid, n (%)										
Intramural	23 (76.7)	13 (81.3)	26 (74.3)	14 (77.8)	24 (75.0)	21 (63.6)	11 (68.8)	18 (60.0)	23 (67.6)	12 (44.4)
Subserosal	5 (16.7)	1 (6.3)	7 (20.0)	3 (16.7)	7 (21.9)	10 (30.3)	2 (12.5)	7 (23.3)	6 (17.6)	12 (44.4)
Non-pedunculated	2 (6.7)	2 (12.5)	1 (2.9)	1 (5.6)	1 (3.1)	2 (6.1)	3 (18.8)	3 (10.0)	4 (11.8)	2 (7.4)
Other[a]	0	0	1 (2.9)	0	0	0	0	0	1 (2.9)	1 (3.7)
UFS-QoL score, mean (SD)										
Symptom severity	59.0 (21.2)	53.6 (20.0)	57.1 (20.3)	63.7 (21.5)	60.3 (21.5)	60.4 (23.3)	72.8 (15.8)	63.3 (18.3)	61.2 (17.1)	58.3 (19.8)
HRQL total	44.5 (20.9)	45.0 (24.6)	38.4 (24.9)	33.0 (20.8)	42.2 (22.6)	40.6 (25.3)	29.9 (22.4)	43.2 (20.6)	40.2 (22.7)	41.2 (29.8)

Note: BID = twice daily; BMI = body mass index; CEP = E_2 1 mg continuously and cyclical oral P 200 mg; E = elagolix (doses in mg); E_2/NETA = E_2 0.5 mg and norethindrone acetate 0.1 mg continuously; HRQL = health-related quality of life; MBL = menstrual blood loss; PBO = placebo; QD = once daily; TDD = total daily dose of elagolix; UFS-QoL = Uterine Fibroid Symptom Quality of Life.

[a] Including pedunculated, submucosal, and other.

Archer. Elagolix for HMB with fibroids. Fertil Steril 2017.

The alkaline hematin method (26) was used for the assessment of MBL. Sanitary products were collected at screening and for any spotting or bleeding episodes that occurred during treatment. Additionally, electronic daily bleeding diary (eDiary) data were used from screening through 3 months after treatment to assess bleeding patterns, using the validated Mansfield-Voda-Jorgenson Menstrual Bleeding Scale (29) for this purpose. This diary included six bleeding categories, as described by Mansfield et al (29).

Safety endpoints included incidence and severity of adverse events (AEs), including AEs of special interest (e.g., hypoestrogenic AEs; osteoporosis and osteopenia; anaphylactic reaction; severe cutaneous adverse reactions and drug-induced rash; depression and suicide or self-injury), clinical laboratory assessments, including lipid panel, and clinically meaningful changes in ultrasound evaluation (e.g., ovarian cysts). Adverse event severity was rated by the investigator. In addition, serum samples for E_2 measurements were collected at screening and every study visit during the treatment period. Patients were required to use two effective, nonhormonal contraception methods (dual contraception), unless this was unnecessary because of sterilization or abstinence. Pregnancy tests were conducted at every study visit, including through the follow-up visit at month 3.

Statistical Analysis

The investigators, participants, and study personnel were blinded to treatment assignment in the placebo-controlled cohorts. Continuous efficacy endpoints for the placebo-controlled cohorts were analyzed to compare each elagolix dosage group with placebo using a 1-way analysis of covariance, with treatment as the factor and baseline MBL as a covariate. Descriptive statistics were used to analyze cohorts without a placebo control group. Statistical analyses were performed using SAS version 9.2 or higher (SAS Institute). Statistical tests were two-sided; comparisons were considered significant if the P value was $\leq .05$.

RESULTS

Disposition and Baseline Characteristics of Study Participants

The study was conducted between September 2011 and May 2014 at 45 sites in the United States. Study population demographics, baseline clinical characteristics, and disposition are shown in Table 1. The mean age was 41.8 years, and 73.8% of women were black. The mean MBL at baseline was 267 mL; the mean largest fibroid volume was 90 cm^3, and most were intramural or subserosal. Substantial numerical differences were observed among treatment groups at baseline in mean MBL (range, 206–434 mL) and the mean largest fibroid volume (46–149 cm^3), possibly because of the relatively small sample sizes of these groups. A total of 271 women were randomized: 221 received active treatment (160 women received elagolix alone; 61 women received elagolix and an add-back therapy), and 50 received placebo (Supplemental Fig. 2). A total of 228 women (84.1%) completed the study, with similar rates across treatment groups (Table 1 and Supplemental Fig. 2).

Efficacy

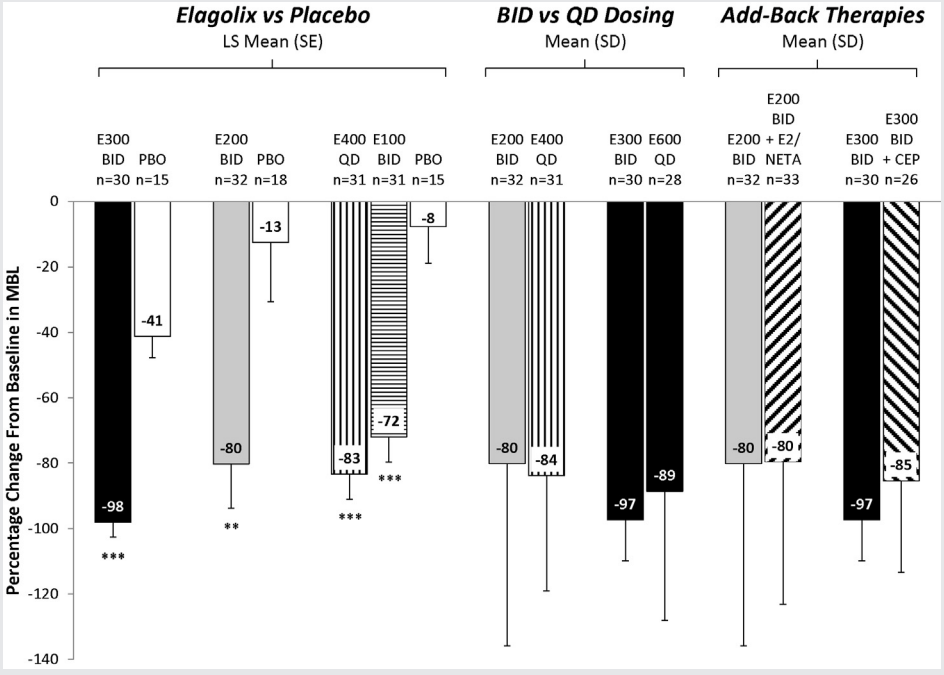
Uterine bleeding endpoints. Women randomized to receive elagolix experienced significantly greater percentage reductions from baseline to last complete treatment cycle in MBL compared with placebo ($P<.01$; last 28 days; Fig. 1). Similar statistically significant effects vs. placebo were observed in mean change from baseline in MBL to last complete treatment cycle (last 28 days; Table 2) and the percentage of women with documented reduction in MBL to <80 mL at last complete treatment cycle and ≥50% from baseline (74%–97% to last complete treatment cycle in elagolix-treated groups vs. 13%–33% in placebo groups; $P<.001$; Supplemental Table 1). Heavy menstrual bleeding as assessed by the alkaline hematin method showed a numerically dose-dependent suppression by elagolix, with the most robust overall suppression at the 300 mg BID dose (Fig. 1 and Supplemental Table 1). At the same TDD, the twice-daily dosing frequency resulted in similar or numerically greater reductions in MBL than once-daily dosing; the addition of add-back therapies to elagolix resulted in similar but numerically smaller reductions in MBL than elagolix alone (Fig. 1, Table 2, and Supplemental Table 1). It should be noted that comparisons of arms that were not placebo-controlled (elagolix 600 mg QD, both add-back arms) are descriptive only because no statistical testing was performed.

Daily eDiary assessments were generally consistent with those assessed with the alkaline hematin method. Compared with placebo, all elagolix dose groups showed a significant reduction in mean percentage of any bleeding days at month 3, with more robust effects on moderate to very heavy bleeding days (Supplemental Table 2). There was a numerically dose-dependent effect of elagolix alone on rates of amenorrhea and suppression of bleeding during the last 8 weeks of treatment, most prominently for elagolix 300 mg BID and 600 mg QD (Supplemental Table 3). However, elagolix plus add-back therapy, compared with elagolix alone, was associated with numerically lower rates of amenorrhea and bleeding suppression. At month 3, both elagolix plus add-back therapy regimens also numerically reduced the percentage of moderate to very heavy bleeding days compared with baseline but numerically increased the percentage of any bleeding days and spotting days (Supplemental Table 2) compared with baseline and elagolix alone. Numerically, the percentages of women with moderate to very heavy bleeding in both elagolix plus add-back dose regimens were lower than those in the placebo groups (Supplemental Table 4).

A majority of women in each elagolix (84.4%–96.8%) and placebo (93.3%–100.0%) treatment group returned to menses within 90 days of the last dose of study drug; the median time to return of menses ranged from 25 to 30 days in the elagolix dose groups and 11 to 19 days in the placebo groups.

Hemoglobin. By multiple measures, hemoglobin levels were improved after elagolix treatment. A higher proportion of women in the elagolix-alone dose groups, compared with placebo, achieved a prespecified increase of ≥1.0 g/dL in hemoglobin from baseline to month 3; add-back therapy had limited effects compared with elagolix alone (Supplemental Fig. 3A). Mean changes from baseline to month 3 in

FIGURE 1



Mean percentage change from baseline in MBL during the last 28 days of treatment. BID = twice daily; CEP = E_2 1 mg continuously and cyclical oral P 200 mg; E = elagolix (doses in mg); E_2/NETA= E_2 0.5 mg and norethindrone acetate 0.1 mg continuously; LS = least squares; MBL = menstrual blood loss; PBO = placebo; QD = once daily; SD = standard deviation; SE = standard error. $^{**}P \leq .01$; $^{***}P \leq .001$. *P* values are for difference in LS mean change from baseline vs. PBO and are derived from an analysis of covariance with treatment as a factor and baseline as a covariate. Descriptive statistics were used to summarize results for cohorts without a PBO control group.

Archer. Elagolix for HMB with fibroids. Fertil Steril 2017.

TABLE 2

Menstrual blood loss measured by the alkaline hematin method during the last 28 days of treatment.

Treatment group	Baseline (mL), mean	Last 28 d (mL), mean (SD)	Change from baseline (mL), mean (SD)	Change from baseline (mL), LS mean (SE)	Difference in LS mean change from baseline (SE) (mL)	*P* value[a]
PBO-controlled						
E300 BID (n = 30)	206	4 (16)	−203 (128)	−237 (21)	−131 (38)	.001
PBO (n = 15)	349	174 (236)	−175 (342)	−106 (30)		
E200 BID (n = 32)	335	59 (179)	−273 (271)	−253 (24)	−138 (41)	.001
PBO (n = 18)	252	173 (118)	−79 (161)	−115 (33)		
E400 QD (n = 31)	214	30 (68)	−184 (132)	−197 (25)	−206 (45)	< .001
E100 BID (n = 31)	269	85 (156)	−185 (187)	−181 (25)	−190 (44)	< .001
PBO (n = 15)	322	311 (365)	−10 (85)	9 (37)		
Not PBO-controlled						
E200 BID (n = 32)	335	59 (179)	−273 (271)			
E400 QD (n = 31)	214	30 (68)	−184 (132)			
E300 BID (n = 30)	206	4 (16)	−203 (128)			
E600 QD (n = 28)	216	27 (94)	−189 (151)			
E200 BID (n = 32)	335	59 (179)	−273 (271)			
E200 BID + E2/NETA (n = 33)	248	55 (140)	−192 (192)			
E300 BID (n = 30)	206	4 (16)	−203 (128)			
E300 BID + CEP (n = 26)	258	42 (96)	−216 (157)			

Note: BID = twice daily; CEP = estradiol 1 mg continuously and cyclical oral progesterone 200 mg; E = elagolix (doses in mg); E_2 /NETA = estradiol 0.5 mg and norethindrone acetate 0.1 mg continuously; LS = least squares; PBO = placebo; QD = once daily; SD = standard deviation; SE = standard error.

[a] *P* value is for difference in LS mean change from baseline vs. PBO and is derived from an analysis of covariance with treatment as a factor and baseline as a covariate. Descriptive statistics were used to summarize results for cohorts without a PBO control group.

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hemoglobin were significantly greater with elagolix alone vs. placebo; however, dosing frequency and add-back therapy did not have clear effects (Supplemental Table 5).

Fibroid and uterine volumes. The majority of elagolix dosing regimens in the placebo-containing cohorts resulted in numerically greater reductions in fibroid volumes (mean change and mean percentage change) from baseline to month 3 compared with placebo (Supplemental Fig. 3B and Supplemental Table 6). Increase in fibroid volume at 3 months after the end of dosing was observed in most elagolix treatment groups compared with placebo groups, although there was high variability (Supplemental Fig. 3C and Supplemental Table 6). Similar to the results for uterine fibroid volume, most elagolix dosing regimens had statistically significantly greater reductions in the mean percentage change in uterine volume compared with placebo, with the largest effects again occurring in the elagolix 300 mg BID dose group (Supplemental Table 7). Co-administration of the add-back therapies generally resulted in numerically smaller reductions in fibroid and uterine volumes relative to administration of elagolix alone.

Quality of life (UFS-QoL). Improvements in the mean change from baseline in UFS-QoL symptom severity scores, as well as health-related quality-of-life (HRQL) total scores and individual HRQL items, were observed at month 3 in most elagolix groups. The elagolix 300 mg BID and 400 mg QD dose groups had significant improvements compared with placebo for both symptom severity and HRQL total scores (Supplemental Table 8). Add-back therapy had an impact that seemed to be numerically more pronounced for elagolix 200 mg BID compared with 300 mg BID.

Estradiol Concentrations

Consistent with the phase 1 hormone data in healthy premenopausal women (17), administration of elagolix resulted in dose-dependent reductions in serum E_2 concentrations, with 200 mg BID and 300 mg BID resulting in median E_2 concentrations of 11 pg/mL through month 2 (Supplemental Table 9). With add-back therapies, numerically higher E_2 concentrations were observed, with median E_2 concentrations of 22 to 23 and 42 pg/mL, respectively, for the elagolix 200 mg BID plus low-dose E_2/NETA and elagolix 300 mg BID plus E_2/cyclical EP groups. Median E_2 concentration was higher with placebo (55–91 pg/mL).

Safety

Treatment-emergent AEs were reported in 70.0%–81.3% of women who received elagolix alone (Table 3), with no apparent relationship to total daily dosage or frequency, and in 56.0% of women who received placebo. In the groups receiving elagolix in combination with add-back therapies, overall rates of treatment-emergent AEs were numerically lower, ranging from 55.6% to 70.6%. Treatment-emergent serious AEs (SAEs) were reported in eight women: five who received elagolix regimens and three who received placebo (Table 3). Only one woman had SAEs considered possibly related to treatment (elagolix 100 mg BID; fibroid necrosis and acute uterine hemorrhage due to prolapsed fibroid resulting in hysterectomy).

Most treatment-emergent AEs were mild or moderate in severity. Twenty women (9.0%) receiving elagolix discontinued study drug because of AEs, which included hot flush (n = 9 [4.1%]) and headache (n = 3 [1.4%]); AEs led to study drug

TABLE 3

Treatment-emergent AEs.

	600 mg TDD			400 mg TDD			200 mg TDD		
Adverse event	**300 BID (n = 30)**	**600 QD (n = 30)**	**300 BID + CEP (n = 27)**	**200 BID (n = 35)**	**400 QD (n = 32)**	**200 BID + E2/NETA (n = 34)**	**100 BID (n = 33)**	**All elagolix (n = 221)**	**PBO[a] (n = 50)**
Any AE	21 (70.0)	22 (73.3)	15 (55.6)	28 (80.0)	26 (81.3)	24 (70.6)	24 (72.7)	159 (71.9)	28 (56.0)
AE possibly related[b]	19 (63.3)	20 (66.7)	11 (40.7)	24 (68.6)	24 (75.0)	16 (47.1)	19 (57.6)	133 (60.2)	15 (30.0)
Serious AE	1 (3.3)	2 (6.7)	0	0	0	0	2 (6.1)	5 (2.2)	3 (6.0)
Severe AE	2 (6.7)	3 (10.0)	3 (11.1)	3 (8.6)	5 (15.6)	0	3 (9.1)	19 (8.6)	5 (10.0)
AE leading to discontinuation	2 (6.7)	3 (10.0)	0	5 (14.3)	4 (12.5)	2 (5.9)	4 (12.1)	20 (9.0)	4 (8.0)
AE in ≥10% women[c]									
Hot flush	15 (50.0)	15 (50.0)	5 (18.5)	19 (54.3)	20 (62.5)	9 (26.5)	15 (45.5)	98 (44.3)	6 (12.0)
Headache	6 (20.0)	9 (30.0)	2 (7.4)	3 (8.6)	4 (12.5)	5 (14.7)	3 (9.1)	32 (14.5)	3 (6.0)
Abdominal pain	3 (10.0)	2 (6.7)	4 (14.8)	2 (5.7)	1 (3.1)	0	1 (3.0)	13 (5.9)	1 (2.0)
Dizziness	3 (10.0)	6 (20.0)	1 (3.7)	2 (5.7)	3 (9.4)	3 (8.8)	1 (3.0)	19 (8.6)	2 (4.0)
Nausea	2 (6.7)	9 (30.0)	4 (14.8)	3 (8.6)	5 (15.6)	1 (2.9)	0	24 (10.9)	3 (6.0)
Back pain	2 (6.7)	5 (16.7)	1 (3.7)	3 (8.6)	3 (9.4)	0	1 (3.0)	15 (6.8)	2 (4.0)
Anemia	1 (3.3)	0	1 (3.7)	1 (2.9)	0	0	2 (6.1)	5 (2.3)	5 (10.0)
Diarrhea	1 (3.3)	3 (10.0)	3 (11.1)	1 (2.9)	1 (3.1)	0	0	9 (4.1)	1 (2.0)
Fatigue	1 (3.3)	2 (6.7)	1 (3.7)	2 (5.7)	4 (12.5)	4 (11.8)	1 (3.0)	15 (6.8)	1 (2.0)
Hypertension	1 (3.3)	3 (10.0)	0	0	0	1 (2.9)	0	5 (2.3)	1 (2.0)

Note: Values are number (percentage). AE = adverse event; BID = twice daily; CEP = estradiol 1 mg continuously and cyclical oral progesterone 200 mg; E_2 /NETA = estradiol 0.5 mg and norethindrone acetate 0.1 mg continuously; PBO = placebo; QD = once daily; TDD = total daily dose of elagolix.

[a] Placebo data from three separate cohorts were pooled.

[b] As assessed by the investigator.

[c] In any treatment group.

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discontinuation in four women (8.0%) who received placebo, including three (6.0%) who had AEs of anemia (Table 3). Two women (one who received elagolix 300 mg BID and one who received elagolix 600 mg QD) were discontinued because of elevations in liver function test results (aspartate transaminase and alanine aminotransferase).

Hot flush was the most commonly reported AE in the elagolix-alone groups, with an incidence of 45.5%–62.5%, compared with 12.0% of women in placebo groups. Hot flush was numerically less frequent when elagolix was co-administered with add-back therapy (26.5% with low-dose E_2/NETA and 18.5% with cyclical EP). Most hot flush episodes were mild in severity. All other AEs in categories of special interest were not serious and were mild or moderate in severity (except one case of severe depression in a participant who received placebo). No participants had events in the category of severe cutaneous adverse reaction. Headache occurred in 20.0% and 30.0% of patients receiving elagolix 300 BID and 600 mg QD alone, respectively, and in 6.0%–14.7% of patients receiving other doses or placebo. Dizziness and nausea were reported in 20.0% and 30.0%, respectively, of patients receiving elagolix 600 mg QD and in 3.7%–10.0% and 2.9%–14.8%, respectively, of patients in other treatment groups. Other AEs occurred with low frequency, so that it was difficult to discern trends.

Administration of elagolix after 3 months resulted in statistically significant mean percentage increases in total cholesterol (14%–20%), triglycerides (13%–41%), and low-density lipoprotein cholesterol (LDL-C; 18%–25%), which were also dose dependent (Supplemental Table 10). Generally there were greater mean percentage increases in high-density lipoprotein cholesterol (HDL-C) for elagolix treatment arms relative to placebo, such that key lipid ratios (e.g., total cholesterol/HDL-C and LDL-C/HDL-C) were minimally impacted. Increases in lipid parameters typically occurred early in treatment (during the first month) and then stabilized. There was a numerical trend toward improvements in lipid parameters in both add-back therapy groups compared with elagolix-alone treatment. There were no meaningful changes in laboratory parameters other than increases in hemoglobin concentrations in elagolix groups.

One woman who received elagolix 600 mg QD had a positive pregnancy test result on day 50, 16 days after her last dose of elagolix, despite the requirement to use effective dual contraception; she elected to have an abortion.

DISCUSSION

Previous phase 1 and 2 studies in healthy women showed that a BID regimen of elagolix more effectively suppressed the pituitary–ovarian axis than a corresponding QD regimen (17, 18). This proof-of-concept, dose-ranging study evaluated 200 mg, 400 mg, and 600 mg TDDs of elagolix using both QD and BID dosing frequency. This study also evaluated the effects of 2 low-dose, oral E_2/progestogen add-back regimens approved for the treatment and prevention of osteoporosis in postmenopausal women.

The demographic characteristics of women in this study, especially the large percentage of black women, are consistent with the affected population of women with fibroids in the United States (1, 30). Growing evidence indicates that fibroids disproportionately affect African American women, who have more severe symptoms, higher incidences of anemia and hysterectomy, and earlier occurrence of hysterectomy compared with white women in the United States (31–33).

All groups treated with elagolix alone showed substantial reductions in HMB, which were statistically significant in the cohorts that included placebo. However, because differences in baseline mean MBL were observed across different cohorts, likely related to the fairly small sample size for each group, comparisons of mean changes in MBL from baseline between different cohorts should be interpreted cautiously. The mean percentage change from baseline in MBL seems to provide a more than adequate representation of numerical differences between various elagolix-containing regimens. Overall, the numerically largest effect on HMB and the highest responder status for the composite bleeding endpoint (97%; Supplemental Table 1) were observed in the elagolix 300 mg BID dose group. Consistent with these results, eDiary findings showed the numerically highest amenorrhea and suppression of bleeding rates in the elagolix 300 mg BID and 600 mg QD dose groups. Overall, these observations indicate the dose-dependent effects of elagolix on bleeding parameters, with the most numerically robust efficacy at the 300 mg BID dose. There was no correlation between the amount of bleeding at baseline and efficacy of elagolix assessed by the alkaline hematin method (data not shown), suggesting that the improvement in bleeding is mostly due to ovarian suppression and subsequent endometrial effects. The effect of elagolix on bleeding was evident at the first efficacy analyses at 2 months, consistent with the rapid suppression of pituitary and ovarian hormones observed previously (17).

The reduction in HMB was associated with increased hemoglobin concentrations in all elagolix groups at month 3. Most women in all elagolix groups (except the low-dose add-back group) had clinically relevant increases in hemoglobin concentrations ≥ 1.0 g/dL, which is approximately equivalent to receiving 1 U of packed red cell transfusion (34). Women treated with elagolix also had improvements in UFS-QoL scores; changes in symptom severity and total HRQL scores were statistically significant for two elagolix doses vs. placebo.

The second objective of this study was to evaluate the safety and efficacy of elagolix in combination with hormonal add-back therapy. Because administration of elagolix alone at doses that provide "nearly full" ovarian suppression for >6 months could be associated with continued vasomotor symptoms and a progressive decrease in bone mineral density (BMD), add-back therapy may be one option for longer-term treatment. Co-administration of either add-back regimen, relative to elagolix alone, resulted in generally similar or slightly lower efficacy in reduction of HMB and responder status for composite bleeding endpoints as assessed by the alkaline hematin method.

Elagolix plus add-back therapy, compared with elagolix alone, was associated with numerically lower rates of amenorrhea and bleeding suppression as assessed by the eDiary. The numerically increased frequency of light bleeding and

spotting during co-administration of elagolix with add-back regimens is consistent with the bleeding pattern of continuous combined E_2/NETA regimens in postmenopausal women during the initial treatment period (35) and cyclical EP regimens, which generally lead to regular withdrawal bleeding but also some irregular bleeding episodes (36).

Treatment with elagolix alone was associated with reductions in fibroid and uterine volumes, with the 300 mg BID dosing regimen producing a significant reduction (36% mean reduction vs. mean increase of 7% with placebo) in the largest fibroid. However, these effects were highly variable, possibly because of a relatively small sample size for each cohort and variability in the quality of the ultrasound images among the study sites. In general, taking into account the limitations of the present data, the fibroid and uterine volume reductions seemed similar to those observed during preoperative treatment with GnRH agonists (37) and to the effects observed in 3-month studies with the selective P receptor modulators asoprisnil and ulipristal acetate (11, 14, 15). A strength of the study design was the use of add-back therapy in several groups, which allowed demonstration that co-administration of either add-back regimen resulted in smaller reductions in fibroid and uterine volumes relative to administration of elagolix alone. Importantly, the low-dose add-back therapy did not seem to negatively affect the efficacy of elagolix on HMB reduction, possibly implying an ovarian contribution to the HMB.

The safety and tolerability of elagolix in this study were consistent with its mechanism of action (i.e., hypoestrogenic effects), the add-back therapies, and previous studies. Rates for SAEs and AEs leading to discontinuation were generally low and not dose-dependent. Overall, AE rates were similar across treatment groups, except for dose-dependent effects on hypoestrogenic events of hot flushes, which was the most frequent AE in elagolix-alone groups (45.5%–62.5%) vs. placebo (12%) and headache, as well as possible elevations of dizziness and nausea with the highest once-daily dose of elagolix. Both low-dose add-back regimens co-administered with elagolix numerically reduced hot flush rates by approximately half compared with elagolix alone. Although changes in BMD were assessed in this study as an exploratory parameter, these results are not reported here because of the short duration of this study and a relatively small sample size per group. A previous study with the GnRH agonist leuprolide acetate showed that a trial of 6 months duration is sufficient to assess changes in BMD (38). The effects of elagolix, with and without add-back therapy, on BMD are being assessed in detail in longer-term completed and ongoing studies of at least 6 months duration, with treatment group sample sizes at least twice those of the present study, and with rigorous assessment of BMD by central readers.

Administration of elagolix alone for 3 months resulted in statistically significant, dose-dependent mean percentage increases in total cholesterol, triglycerides, and LDL-C (13%–41%; Supplemental Table 10). These anticipated hypoestrogenic effects are also observed in postmenopausal women (39) and with other agents that suppress E_2. However, HDL-C values increased with elagolix, thus minimizing net changes to key lipid ratios. Both add-back therapy regimens partially numerically mitigated these effects. Elagolix plus low-dose E_2/progestogen add-back therapy may represent an additional long-term treatment option for women with HMB and uterine fibroids. Longer phase 3 studies, which are currently underway, will be needed to establish the long-term efficacy and safety of this regimen and assess its potential advantages and disadvantages vs. current treatment regimens, including long-term intermittent use of ulipristal acetate (16), which has been approved in the European Union.

One strength of this study was the comprehensive dose-ranging design, which evaluated a range of TDDs with and without add-back therapies. The use of the quantitative alkaline hematin method for bleeding assessment also contributed to the robustness of the findings. However, randomized comparisons vs. placebo were available only for some cohorts; thus, conclusions about safety and efficacy are less relevant for uncontrolled treatment regimens. No formal comparisons were made between treatment cohorts. Alkaline hematin data were not collected during the follow-up period, so recurrence of bleeding after the cessation of treatment cannot be assessed; however, the time to return of menses was recorded. Further, changes in BMD and the effects of elagolix on the endometrium are currently being evaluated in studies of longer treatment duration.

In conclusion, this study demonstrated numerically dose-dependent improvement of HMB with elagolix in women with fibroids, most robustly with the 300 mg BID dose. The low-dose add-back regimens had marginal effects on HMB endpoints and substantially reduced the frequency of hot flushes. These results provide a rationale for phase 2b and 3 clinical trials of longer duration to further evaluate the safety and efficacy of elagolix with add-back regimens as a potential chronic treatment for uterine fibroids in women experiencing HMB.

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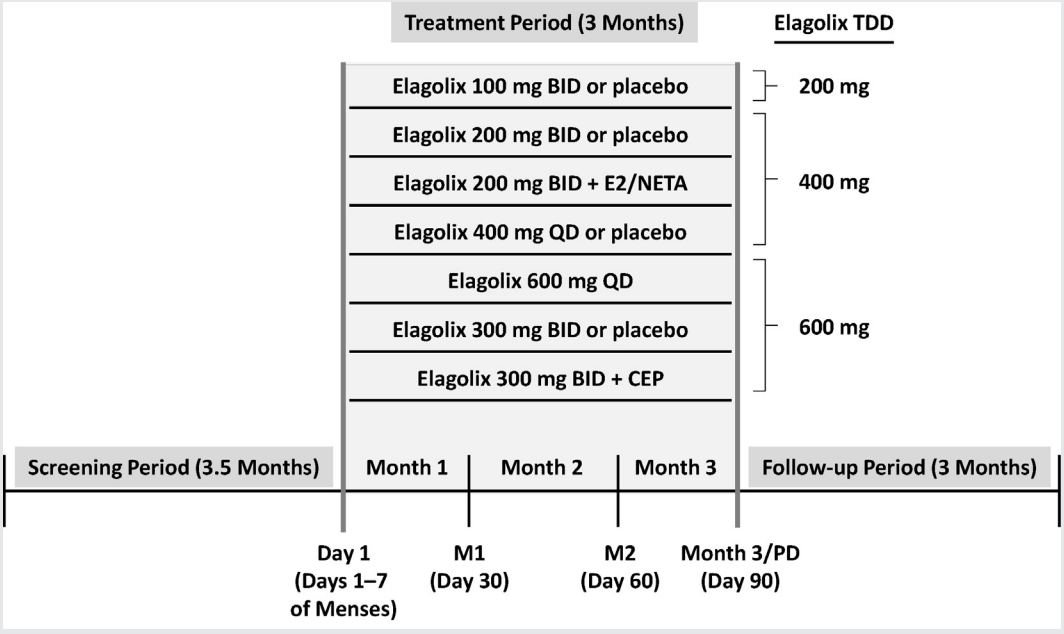
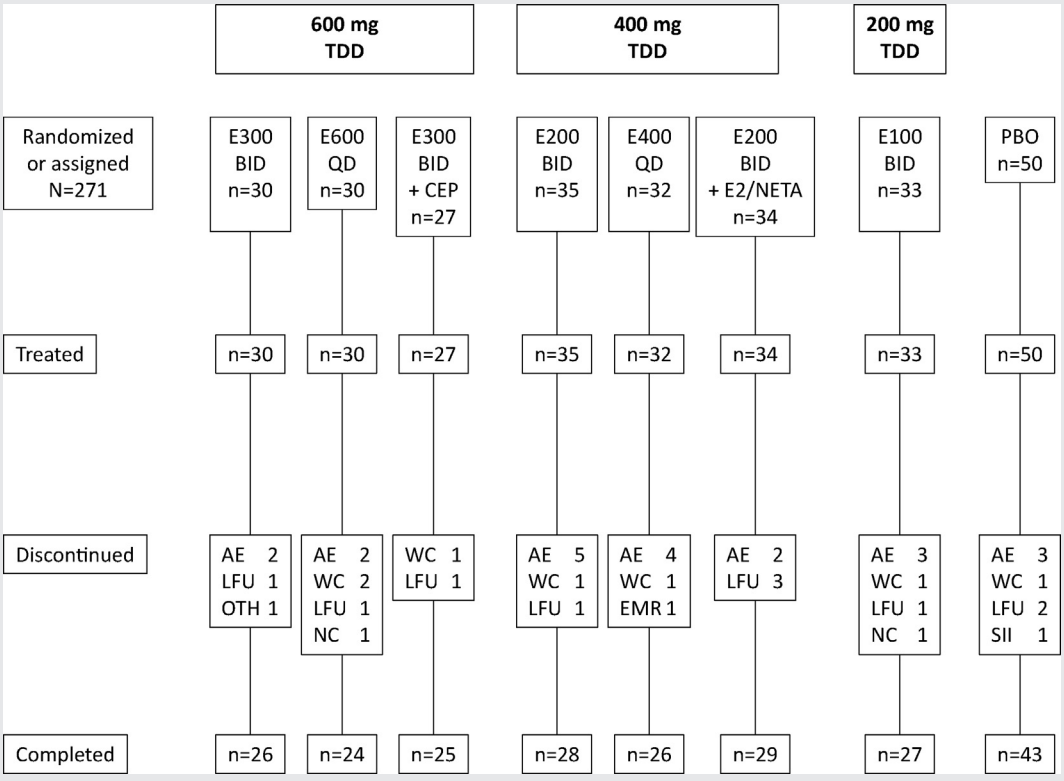
SUPPLEMENTAL FIGURE 1



Study design. BID = twice daily; CEP = E_2 1 mg continuously and cyclical oral P 200 mg; E2/NETA = E_2 0.5 mg and norethindrone acetate 0.1 mg continuously; M1 = end of month 1 visit; M2 = end of month 2 visit; QD = once daily; PD = postdose; TDD = total daily dose.

Archer. Elagolix for HMB with fibroids. Fertil Steril 2017.

SUPPLEMENTAL FIGURE 2



Study disposition. AE = adverse event; BID = twice daily; CEP = E_2 1 mg continuously and cyclical oral P 200 mg; E = elagolix (doses in mg); EMR = exclusionary medication received; E2/NETA = E_2 0.5 mg and norethindrone acetate 0.1 mg continuously; LFU = lost to follow-up; NC = not compliant; OTH = other; PBO = placebo; QD = once daily; SII = surgery or invasive intervention; TDD = total daily dose; WC = withdrew consent.

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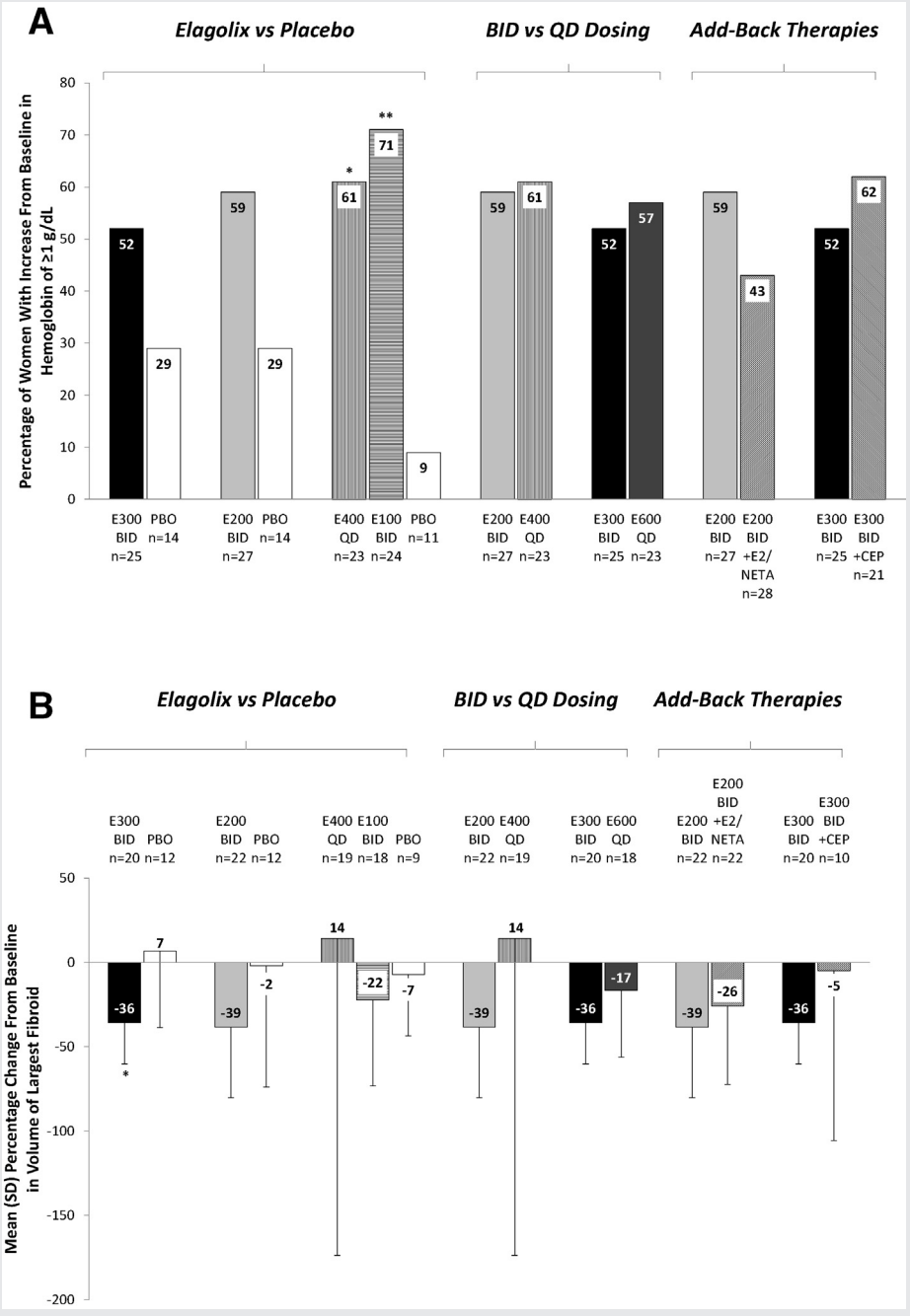
SUPPLEMENTAL FIGURE 3



Hemoglobin and fibroid volume results. (**A**) Percentage of women with ≥1.0-g/dL increase from baseline in hemoglobin at month 3. (**B**) Mean percentage change from baseline to month 3 in the volume of the largest uterine fibroid.

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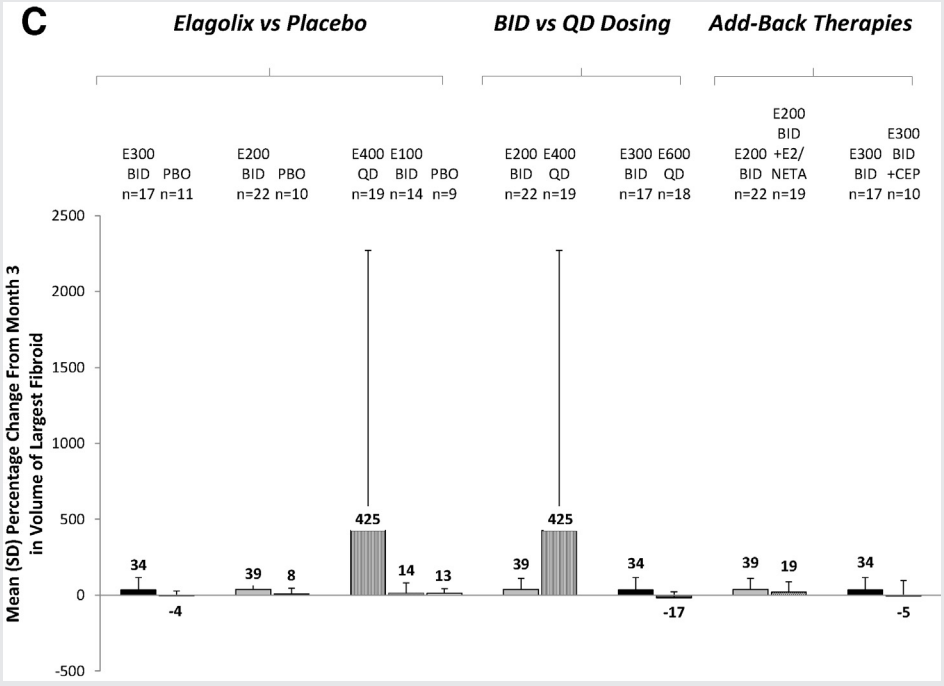
SUPPLEMENTAL FIGURE 3 Continued



(**C**) Mean percentage change from month 3 to posttreatment month 3 in the volume of the largest uterine fibroid. BID = twice daily; CEP = E_2 1 mg continuously and cyclical oral P 200 mg; E = elagolix (doses in mg); E2/NETA= E_2 0.5 mg and norethindrone acetate 0.1 mg continuously; PBO = placebo; QD = once daily; SD = standard deviation. *$P \leq .01$; **$P \leq .001$. Descriptive statistics were used to summarize results for cohorts without a PBO control group; no statistical testing was performed for changes from month 3 to posttreatment month 3.

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