Effective and Rapid Control of Bleeding with Elagolix with or without Add-Back Therapy in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids

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Introduction: Elagolix, an oral gonadotropin-releasing hormone antagonist, with and without add-back therapy, was evaluated in premenopausal women with heavy menstrual bleeding (HMB; monthly blood loss [MBL] > 80mL per cycle) associated with uterine fibroids (UF).
Methods: This double-blind, randomized, placebo-controlled, parallel group study (NCT01817530) evaluated the efficacy and safety of 6 months of treatment in 2 cohorts: elagolix 300mg twice daily in cohort 1 (C1) and 600mg once daily in cohort 2 (C2). Each cohort had 4 arms: placebo, elagolix alone, and 2 elagolix add-back arms (Low dose [LDA], estradiol [E2] 0.5 mg/norethindrone acetate 0.1 mg [NETA], or standard dose [SDA], 1.0mg E2/0.5mg NETA). MBL volume was assessed using alkaline-hematin-method (months 3-6) and heavy bleeding days were recorded in a daily electronic bleeding diary (months 1- 6) in women with at least 28 days of treatment. Quality of life (QoL) measures were assessed using the Uterine Fibroid Symptom and QoL (UFS-QoL) questionnaire. Adverse event (AE) reporting, standard laboratory parameters, and changes in bone mineral density (BMD) were assessed.
Results: In C1, 259 women were randomized and treated; 80% completed treatment. The effects on HMB were rapid as evidenced by a significant reduction in the number of heavy bleeding days on days 29-56 of treatment in all elagolix groups vs. placebo (LS mean [SE] change from baseline to month 2: elagolix alone= -1.7 [0.25], elagolix+LDA= -1.6 [0.22], elagolix+SDA= -1.4 [0.20], placebo= -0.8 [0.18]; each $p<0.05$ vs. placebo). During the final 28 days of treatment, 92%, 89%, 79%, and 33% of women had MBL< 80 mL and 94%, 87%, 82% and 31% of women had an MBL volume reduction from baseline of ≥ 50% in the elagolix alone (n=62), elagolix + LDA (n=61), elagolix + SDA (n=62), and placebo (n=64) groups, respectively ($p<0.001$, all elagolix groups vs. placebo). All elagolix treatments were associated with improved QoL. Elagolix treatment alone was associated with hypoestrogenic effects, such as hot flushes and decreases in BMD. Add-back therapy attenuated hot flushes and lumbar spine BMD decreases in a dose-dependent manner (mean [95% CI] percentage change from baseline to month 6 in lumbar spine BMD: elagolix alone= -3.8 [-4.6, -3.0], elagolix + LDA= -1.6 [-2.4, -0.85], elagolix + SDA= -0.14 [-0.92, 0.63], placebo= 0.91 [0.10, 1.7]; all $p<0.05$ vs placebo except elagolix + SDA which was not significant). Results were similar in C2.
Conclusions/Implications: Elagolix (with or without add-back) effectively and rapidly reduced HMB and improved QoL in women with UF. NETA add-back therapy attenuated the hypoestrogenic effects (hot flushes and BMD decreases) of elagolix in a dose-dependent manner with marginal effects on efficacy.

Keywords : uterine fibroids, elagolix, oral non-peptide GnRH antagonist, leiomyomata, heavy menstrual bleeding, add-back therapy, bone mineral density, clinical trial
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