ObGyn Article Summary

This article comprised of 2 randomized, double-blind, multicenter, placebo-controlled phase III trials done to evaluate the efficacy of elagolix, an oral GnRH antagonist, for controlling both dysmenorrhea and nonmenstrual pelvic pain. Subjects eligible to participate were premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain. Two double-blind, randomized, 6-month phase 3 trials (Elaris Endometriosis I and II [EM-I and EM-II]) were performed to evaluate the effects of two doses of elagolix — 150 mg once daily (lower-dose group) and 200 mg twice daily (higher-dose group) — as compared with placebo in these women.

Women underwent randomization for Elaris EM-I at 151 sites in the United States and Canada from July 2012 through May 2014 and for Elaris EM-II at 187 sites on five continents from November 2013 through July 2015. Each trial was divided into four intervals: a washout of hormonal therapies (if applicable); a screening period of up to 100 days, including two menstrual cycles, during which women switched from the use of usual analgesic agents to receive allowed rescue medication of an NSAID (500 mg of naproxen), an opioid according to country (e.g., 5 mg of hydrocodone plus 325 mg of acetaminophen), or both; a 6-month treatment period; and a follow-up period of up to 12 months, unless the woman was enrolled in the corresponding 6-month extension study.

The two primary outcomes were the proportion of women who had a clinical response with respect to dysmenorrhea and the proportion who had a clinical response with respect to nonmenstrual pelvic pain at 3 months. The key secondary outcomes were the mean changes from baseline to 3 months or 6 months, which were tested in the following order: the score on the Numeric Rating Scale (0 [no pain] to 10 [worst pain ever]) at 3 months, dysmenorrhea at 6 months, nonmenstrual pelvic pain at 6 months, use of rescue analgesic agents (both NSAID and opioid pill counts) at 3 months and 6 months, dyspareunia (0 [none] to 3 [severe] or not applicable) at 3 months, and the use of a rescue opioid at 3 months.

A total of 872 women underwent randomization in Elaris EM-I and 817 in Elaris EM-II; of these women, 653 (74.9%) and 632 (77.4%), respectively, completed the intervention. The results showed that those who received two different doses of elagolix had significantly lower scores for dysmenorrhea and nonmenstrual pelvic pain than did those who received placebo after 3 months and 6 months of treatment. This was based on the significantly better scores for endometriosis-associated pain on the Numeric Rating Scale at 3 months among those who received elagolix than those who received placebo. In addition, women who received the higher dose of elagolix (200 mg twice daily) had significantly better results with respect to the use of rescue analgesic agents at 3 months and 6 months, dyspareunia at 3 months, and rescue opioid use at 3 months than did those receiving placebo. However, the women who received elagolix experienced the hypoestrogenic effects of the drug. They had higher rates of hot flushes, higher levels of serum lipids, and greater decreases from baseline in bone mineral density than did those who received placebo. The shift in the lipid profile with elagolix treatment included both increased HDL cholesterol levels but also increased LDL cholesterol levels, which may raise concern for long-term cardiovascular risk. There were no adverse effects on the endometrium after 6 months of

elagolix treatment. Results also showed that women in the higher-dose group had a greater reduction in pain and more severe hypoestrogenic adverse effects than those in the lower-dose group, which suggests the possibility of individual tailoring of these two doses to balance efficacy with hypoestrogenic effects. Although these results were promising, further evaluation is warranted to better assess the risk–benefit profiles of each dose.