Drug Evaluation

Women's Health

Elagolix, a novel, orally bioavailable GnRH antagonist under investigation for the treatment of endometriosis-related pain

Suppression of estrogen production and reduction of menstrual blood flow are the mainstays of medical treatment of endometriosis-related pain and have been traditionally achieved by methods such as combined hormonal contraception, progestins and GnRH analogs, all with comparable efficacies, though different side-effect profiles. Elagolix is the frontrunner among an emerging class of GnRH antagonists, which unlike their peptide predecessors has a nonpeptide structure resulting in its oral bioavailability. Phase I and II clinical trials have demonstrated safety of elagolix and its efficacy in partial and reversible suppression of ovarian estrogen production resulting in improvements in endometriosis-related pain. Phase III clinical trials are currently underway and elagolix may become a valuable addition to the armamentarium of pharmacological agents to treat endometriosis-related pain.

Keywords: bone mineral density • elagolix • endometriosis • GnRH antagonists • medical treatment

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Endometriosis is a debilitating disease that affects about 5–10% of reproductive age women [1–3]. From a histological perspective, it is defined by the presence of endometrial glands and stroma outside of the uterine cavity, most commonly in the peritoneal cavity affecting dependent areas of the pelvis such as posterior cul-de-sac, ovaries and bowels [4]. Similar to eutopic endometrium, these ectopic endometrial implants undergo cyclic changes in response to ovarian steroids, mainly estrogen and to a much lesser extent, progesterone as there is significant progesterone resistance in these tissues [4]. These cyclic transformations in areas that are not physiologically equipped to clear endometrial sheddings lead to a chronic inflammatory state called endometriotic disease that most commonly manifests itself with pain and/or infertility. Pain associated with endometriosis can have many different forms but it is usually expressed as dysmenorrhea, dyspareunia or nonmenstrual pelvic pain. Depending on the anatomic site affected, it can also result in dysuria, dyschezia or even pain outside of the pelvic cavity. In addition to the proinflammatory milieu that results in the irritation of the peritoneal surfaces and subsequently in pain, other mechanisms have been implicated to explain the pain symptoms associated with endometriosis. Deep infiltration of endometriosis into the substance of the uterosacral–cardinal ligament complex and posterior cul-de-sac can result in dyspareunia [5] while a more scattered presence of endometriosis lesions in the peritoneal cavity could result in overproduction of prostaglandins with excessive uterine contraction and dysmenorrhea [6]. Furthermore, there is evidence to suggest that patients with endometriosis may suffer from hyperalgesia due to chronic irritation of the pain fibers in the sensory nerves [7]. However, regardless of the mechanism(s) by which endometriosis causes pain, it is noteworthy to mention that there is little correlation between the extent of the lesions and severity of the symptoms [8]. Diagnosis of endometriosis has traditionally relied on surgical visualization of the lesions with or without subsequent confirmation by

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histology. However, the inevitable implication of this diagnostic strategy is to significantly underestimate the prevalence and incidence of the disease, particularly in those with mild to minimal symptoms or alternatively individuals with limited access to quality gynecological healthcare. The economic burden of endometriosis is very substantial with weekly cost estimates per woman, merely due to loss of productivity averaging 10 h a week, ranging between US$4 in Nigeria to US$456 in Italy [9]. In a different study, based on annual cost estimates of US$2800 for direct healthcare costs and US$1023 for costs due to loss of productivity per patient, endometriosis was indicted for a US$22 billion annual toll on the US economy [10].

Overview of the market

Management options for endometriosis depend on the type of symptoms attributed to the disease. Treatment of infertility associated with endometriosis is generally based on assisted reproductive technology (ART) and/or surgery [11]. On the other hand, both medical and surgical options are effective in alleviating endometriosis pain, albeit each with its own advantages and limitations [12]. Several clinical trials and systematic reviews have demonstrated the efficacy of surgery in improving endometriosis-associated pain [13]; however, probably the most troublesome disadvantage of surgery is the temporary nature of the resulting pain relief, with some studies quoting a recurrence risk of as high as 60% in 1 year after the primary surgery [1,13], leading to a significant reoperation rate of 50% in 5 years [14]. Another significant disadvantage of surgery is the high risk of complications in cases of rectovaginal or ureteral involvement [15,16]. With regard to medical management, with the exception of nonsteroidal anti-inflammatory drugs and other analgesics, the goals of pharmacotherapy are suppression of ovulation and induction of a relatively hypoestrogenic milieu [12] and/or complete cessation or reduction of menstrual blood flow [1,4]. Several different hormonal therapies have been used to this aim and the options include combined oral contraceptive pills and other forms of combined hormonal contraception, progestogens, androgenic agents such as danazol, GnRH analogs (agonists and antagonists), aromatase inhibitors, gestrinone (an anti-progesterone agent approved in Europe but not available in the USA), mifepristone and levonorgestrel-releasing IUDs [4,12].

Combined oral contraceptive pills have long been the first-line treatment for endometriosis-associated dysmenorrhea and their superior effectiveness compared with placebo is well proven [17,18], particularly when taken in a continuous fashion instead of the traditional cyclic use [19]. Side effects associated with combined hormonal contraception are generally the same as when they are used for contraceptive and other purposes and include increased risk of venous thromboembolism, nausea, fluid retention, depression, weight gain, breast tenderness, headache and one particular problem most commonly encountered with continuous use of oral contraceptive pills (OCPs), increased incidence of breakthrough bleeding [20]. Several different types of progestational agents have been evaluated for the treatment of endometriosis-related pain, particularly for those who do not tolerate or respond to OCPs, or those affected with dyspareunia and nonmenstrual pelvic pain. In addition to possible suppression of follicular development and ovulation, progestins cause decidualization of eutopic and ectopic endometrial tissue, exert anti-inflammatory and anti-angiogenesis effects [21] and inhibit matrix metalloproteinases [22,23]. Most commonly used progestins for this purpose are norethindrone acetate [20,24] and dienogest [25–27], both popular in Europe and Japan, and medroxyprogesterone acetate (MPA) [28], which is most commonly prescribed in the USA. Side effects of progestins are similar to OCPs, with the possible exception of increased risk of venous thromboembolism which is less common with the use of progestins alone. Other options include danazol, a derivative of 17 α-ethinyltestosterone, which works mainly through inhibition of ovulation and suppression of hypothalamic–pituitary–ovarian axis, but is no longer commonly prescribed due to major androgenic side effects (e.g., acne, hirsutism and deepening of the voice) and availability of alternative effective medications [29].

Due to their abilities for complete suppression of the hypothalamic–pituitary–ovarian axis, GnRH agonists have been extensively studied for the treatment of endometriosis and their effectiveness compared with placebo is well proven [30]. However, despite the profound hypoestrogenic state that follows their administration, GnRH agonists have not been shown to be superior to other hormonal treatments for endometriosis pain [31]. In addition, the endocrine milieu associated with prolonged use of GnRH agonists, causes significant short- and long-term hypoestrogenic side effects such as hot flashes, dry vagina, reduction in bone mineral density (BMD) and unfavorable lipid profile [30]. In order to overcome some of these side effects and enable use of GnRH agonists on a longer term basis, add-back therapies with various hormonal agents have been suggested [32,33]. The only US FDA approved agent in the USA for add-back therapy is norethindrone acetate which is partly converted to ethinylestradiol alleviating the effects of estrogen deficiency while its progestogenic actions maintain endometrial decidualization [34,35]. In other parts of the world and particularly in

Europe, tibolone is a popular choice for add-back therapy with long-term use of GnRH agonists [36–38] but this agent is not currently available in the USA. With the exception of one small feasibility study of cetrorelix in only 15 cases [39], there are no clinical data on the efficacy of available injectable, peptide GnRH antagonists, cetrorelix and ganirelix, for the treatment of endometriosis-related pain [18]. Based on our increasing understanding of the pathogenesis of endometriosis implicating local overproduction of estrogens in the ectopic implants through dysregulated expression of aromatase and other mechanisms [40,41], aromatase inhibitors have been studied as a potential therapeutic option for endometriosis-related pain [42]. Efficacy of aromatase inhibitors for pain reduction is comparable to other hormonal therapies but their side-effect profile is slightly different [43], causing less frequent and less severe hot flashes but comparable reduction in BMD as compared with GnRH agonists. Use of aromatase inhibitors in premenopausal women should be accompanied by some form of ovarian suppression with choices such as progestins, OCPs or GnRH analogs as otherwise the concomitant increase in pituitary FSH output results in follicular development and formation of ovarian cysts [42]. Several other agents such as selective estrogen receptor modulators, selective progesterone receptor modulator, anti-inflammatory agents, anti-angiogenesis agents and even statins have been suggested as potential therapeutic options for endometriosis-associated pain [44–46]; however, at least for some drugs, such as raloxifene, the initial promise based on *in vitro* studies was not subsequently delivered in clinical trials [47].

Introduction to elagolix

Considering that all the available medical options for the treatment of endometriosis-associated pain have nearly comparable efficacy and in almost all cases pain symptoms will recur upon discontinuation of therapy, the choice of the treatment has been mainly influenced with the side-effect profile of the medication, particularly when considered for long-term use [4]. On the other hand, although endometriosis is an estrogen-dependent disease, based on the estrogen threshold theory introduced in 1990s [48], complete suppression of endogenous estrogen production is not necessary for obtaining maximal benefit of pain relief when the treatment mechanism is creation of a hypoestrogenic environment. This model is important as it implies that it would be possible to maintain serum estradiol levels in a window (30–45 pg/ml) that is lower than what is required to stimulate the growth of endometriotic implants and yet adequate to mitigate at least some of the hypoestrogenic side effects, such as the effects on BMD, hot flushes and dry vagina. With the above background in mind, the availability of some preclinical data on the effectiveness of GnRH antagonists in suppressing endometriosis lesions in animal models [49–51], has led several investigators to pursue development of GnRH antagonists as an additional therapeutic option for endometriosis-related pain. Potential benefits of GnRH antagonist over GnRH agonists include a more rapid onset of actions without the initial flare up associated with GnRH agonists and a more rapidly reversible mode of action, which allows fine tuning the extent of pituitary suppression [52,53]. As of July 3, 2013, there are at least 15 registered clinical trials on ClinicalTrials.gov [54] that aim to evaluate the efficacy and safety of GnRH antagonists for the treatment of endometriosis-related pain [55]. The vast majority of these trials (14 out of 15) are sponsored by the pharmaceutical industry [55] and in fact trials on this particular class of medications comprise the largest group of trials among industry-sponsored studies (31.1% or 14 out of 45 trials), with the second most popular agents being selective progesterone receptor modulators with 17.8% (eight trials) [55]. Currently marketed GnRH antagonists are all peptide analogs of the GnRH and therefore cannot be taken orally as the protein structure of the molecule undergoes proteolysis in the GI tract before absorption [52]. Among these peptide GnRH antagonists, cetrorelix was evaluated for the treatment of endometriosis-related pain in a clinical trial sponsored by Solvay Pharmaceuticals and conducted in several European countries during 2005–2006; however, the results of this trial have not been published [54]. Another clinical trial on endometriosis-related pain is currently recruiting patients in Italy to evaluate the efficacy of once monthly subcutaneous degarelix (a peptide GnRH antagonist currently approved for prostate cancer) with estimated completion date in October 2014 [54]. With the exception of the above two peptide GnRH antagonists, cetrorelix and degarelix, all the other GnRH antagonist trials are focusing on a new class of these compounds, which are small molecule, nonpeptide GnRH antagonists and therefore have the potential to be administered orally. None of these novel drugs are currently approved for clinical use but four of them, elagolix, KLH-2109, TAK-385 and ASP 1707 are being actively investigated in clinical trials, with elagolix being the only one currently undergoing Phase III trials. The advantages of orally administered GnRH antagonists include a more convenient mode of delivery for patients, avoidance of injection site reactions and hopefully a more practical way to take advantage of the drug's dose-response curve to optimize the risk-benefit ratio. The first orally active nonpeptide GnRH antagonist was described in

1998 [56] and subsequently several other groups have evaluated different compounds as potential candidates [57], examples of which include uracil derivatives elagolix [58] and its parent compound, NBI-42902 [59], a macrolide analog [60], a furamide derivative [61,62], a thienopyrimidine derivative, named TAK-013 [63] and its subsequent modification to TAK-385 [64], and a 4-piperazinylbenzimidazole compound [65]. To date, published human data are only available for NBI-42902 [66], elagolix [67–70] and TAK-013 [71]. For three other nonpeptide, orally bioavailable, GnRH antagonists that are currently undergoing Phase II trials, TAK-385, KLH-2109 and ASP 1707, no published data were found.

Elagolix has been synthesized through a series of structural modifications of its parent compound, a uracil derivative known as NBI-42902, which have led to preservation of its potent GnRH receptor antagonistic activity while minimizing its inhibitory effects on CYP3A4 and potential for significant and unwanted drug–drug interaction [58]. In brief, these steps have involved substitution of a larger moiety at one of the fluorine groups of the 1-benzyl group in the parent molecule to improve its GnRH receptor binding affinity, as well as incorporation of a carboxylic group to reduce its inhibitory effects on CYP3A4 [58]. These modifications have resulted in an equivalent competitive binding affinity for GnRH receptor with elagolix K_i = 0.90 nM versus NBI-42902 K_i = 0.56 nM, but much lower inhibitory effects on CYP3A4, with elagolix IC_{50} = 56 μM versus NBI-42902 IC_{50} = 0.70 μM [58]. Moreover, the potency of the two compounds in inhibiting inositol trisphosphate production in response to GnRH was similar [58]. Additionally, a panel of radioligand competition binding assays for 100 off-target receptors, transporters, ion channels and enzymes was used to test the specificity of elagolix for GnRH receptors and the selectivity of elagolix for GnRH receptor was demonstrated by negligible binding of elagolix to these targets despite being present in very high concentration at 10 μM [58].

Pharmacodynamics

The first human study evaluating the effects of elagolix was published in 2009 reporting its effectiveness in suppression of gonadotropins and estradiol in a randomized, double-blind, placebo-controlled study of 55 healthy premenopausal women [70]. Investigators studied elagolix at various dosing regimens, including an initial phase with single doses of 25, 50, 100, 200 and 400 mg taken orally. Subsequently, once safety was established, manufacturers proceeded to multiple dose regimens with 50, 100 or 200 mg once daily (q.d.) for 7 days, as well as an arm with 100 mg twice daily (b.i.d.) for 7 days. In subjects receiving a single dose of elagolix, regardless of the dosage amount varying between 25 and 400 mg, LH levels rapidly declined to 22–35% of the predose baseline within 4 h of administration. After this peak effect at 4 h, serum LH levels gradually started to return to baseline, with all subjects recovering by 24 h and as expected, the recovery rate was inversely related to the administered dose [70]. Similar suppressive effects were noticed on serum FSH levels, though with a lesser magnitude and slower pace, reaching 62–71% of the baseline after 8–12 h of administration [70]. These differing effects on LH and FSH are explained by the facts that FSH has a longer half-life in the circulation than LH and other hormones such as inhibins, in addition to GnRH, control its secretion [72]. Elagolix administration at 50, 200 and 400 mg resulted in suppression of serum estradiol levels to 42–65% of baseline values after 24 h. There was no reduction in estradiol level with 25 mg and the observed difference at 100 mg was not statistically significant. Estradiol levels in all groups returned to normal in 48 h. Similar results were observed in multiple dose regimens with LH nadir at 4–6 h after administration and near total recovery by 24 h. FSH levels were similarly suppressed with the exception of the group receiving 100 mg b.i.d., which showed a residual suppression at 74% of the baseline in the following morning [70]. Mean serum estradiol levels demonstrated either no change or a significant decrease compared with the baseline in early follicular phase. During the 1-week treatment period, mean estradiol levels in recipients of multiple dose regimens were 17 ± 3 to 68 ± 46 pg/ml, with the highest level of suppression in the 100 mg b.i.d. group. Of note, two women, one in the 100 mg q.d. cohort and one in the 200 mg q.d. cohort, continued to have increasing levels of estradiol during the treatment period despite having serum elagolix levels equivalent to those who showed ovarian suppression [70]. It would be logical to assume that an earlier start of GnRH antagonist in the follicular phase would be more likely to exert a suppressive effect on follicular development and subsequent rise in estradiol levels.

Pharmacokinetics & metabolism

Elagolix is rapidly absorbed through the GI tract following oral administration, reaching its peak plasma concentrations in a dose-dependent manner within 30–60 min [70]. Plasma half-life of elagolix across a range of dosage regimens varies from 2.4 to 6.3 h. The drug is rapidly metabolized and only 3% of the orally administered dose is excreted intact in the urine [70]. The principle metabolite of elagolix has been named NBI-61962 which is unlikely to have any significant

biologic effect due to its low plasma exposure and a potency that is significantly less than elagolix (K_i value of 3.5 vs 0.9 nM).

Clinical efficacy

Safety and clinical efficacy of elagolix has been evaluated in several Phase I and II clinical trials. Phase I study [70] evaluated the safety, pharmacokinetics and pharmacodynamics of the drug and has been discussed in the previous sections. Following the establishment of safety in Phase I study trials, elagolix has undergone several Phase II clinical trials with published results for two trials, Liliac PETAL or NBI 56418–0702 study, and Daisy PETAL or NBI 56418–901 study [73], and an abstract and article in press for PETAL or NBI 56418–603 study [69,74]. Based on the FDA's database and manufacturer's website, there has been another Phase IIb study, Tulip PETAL (NBI-56418–0703 study), as well as two Phase IIa studies which have been completed but no result has been published at the time of writing this review.

In PETAL or NBI 56418–603 study, 252 patients with laparoscopically proven endometriosis, were randomized in three arms, each comprising 84 patients, to receive elagolix 75 mg b.i.d. or elagolix 150 mg q.d. for 6 months, along with a third active control arm with subcutaneous depot medroxyprogesterone acetate (SC-DMPA) administered every 3 months [69,74]. Patients were followed up for another 6 months after completion of the active phase. Primary end point was the effect of elagolix on BMD and secondary end points were assessment of its safety and effectiveness using monthly recall with Composite Pelvic Signs and Symptoms Scale (CPSSS) and Endometriosis Health Profile (EHP-5). Endometriosis-associated pain was assessed more specifically with daily Visual Analog Scale (VAS).

There was no statistically significant difference in BMD as the primary end point among the three arms of the study with all three groups showing only minimal reduction in BMD at spine and hip at the end of week 24 with elagolix 150 mg showing a mean reduction of -0.11% (95% CI: -0.70–0.48) in spine and -0.47% (95% CI: -0.96–0.02) in femur, elagolix 75 mg b.i.d. with mean reduction of -1.29% (95% CI: -1.85 to -0.74) in spine and -1.02% (95% CI: -1.48 to -0.56) in femur and SC-DMPA with -0.99% (95% CI: -1.61 to -0.37) reduction at spine and -1.29% (95% CI: -1.80 to -0.77) in femur [74]. Total CPSSS, VAS and the pain component of EHP-5 were all reported to have significantly improved compared with the baseline, with the majority of patients continuing to report beneficial effects at 6 months after completion of the study. The most commonly occurring side effects were headache and nausea. At the end of 6-month period, mean serum estradiol levels were 45 and 29 pg/ml in 150 mg q.d. and 75 mg b.i.d. cohorts, respectively, which was consistent with Phase I study results showing a more pronounced suppression of gonadal steroid production with b.i.d. dosing.

Following completion of NBI 56418–603 study, FDA recommended using daily pain scores for end points of dysmenorrhea and nonmenstrual pelvic pain which resulted in a modification of the efficacy measures for the subsequent trial using an 11-point numerical rating scale (NRS) for daily assessment of pelvic pain and a modified Biberoglu-Behrman scale [75] for dysmenorrhea and nonmenstrual pelvic pain. Additional efficacy measures were evaluated with CPSSS (dyspareunia component), EHP-5 and Patient Global Impression of Change (PGIC) [76]. In Liliac PETAL or NBI-56418–0702 study, 155 patients with laparoscopically proven endometriosis were randomized to elagolix 150 mg q.d. or elagolix 250 mg q.d., parallel with a third placebo-controlled arm [67]. Of note, after 12 weeks, the placebo group was re-randomized to elagolix 150 mg versus 250 mg q.d. for another 12 weeks. Those randomized to elagolix at the beginning of the trial continued with the active medication (elagolix 150 mg or 250 mg q.d.) for the full 24 weeks. A significant decrease in dysmenorrhea based on the modified Biberoglu-Behrman scale, and dyspareunia based on the CPSSS was observed in both elagolix arms compared with the placebo at weeks 8 and 12. There was also a significant improvement in overall quality of life based on PGIC scores in both elagolix dosage arms as compared with the placebo. However, there was no statistically significant difference in either mean daily pelvic pain assessments based on the NRS, or nonmenstrual pelvic pain based on the modified Biberoglu-Behrman scale. There was also no difference in analgesic use among the three groups and no statistically significant change in EHP-5, despite a numerical trend toward improvement with elagolix [67]. There was a small, but significant reduction in BMD (mean ± standard deviation [SD]: -0.937 ± 2.75%) at the spine after 12 weeks in the cohort receiving 250 mg. After 24 weeks, there was a significant reduction in BMD at spine (mean ± SD: -1.032 ± 1.98 and -1.631 ± 2.87% for elagolix 150 and 250 mg, respectively) and femur (mean ± SD: -0.743 ± 1.88 and -1.024 ± 1.76% for elagolix 150 and 250 mg, respectively) [67].

Subsequently, after no difference in nonmenstrual pelvic pain was observed in Liliac PETAL or NBI-56418–0702 study, in order to improve the sensitivity of the questionnaire, manufacturers discussed the wording of the questionnaire with the FDA and modified it for the next Phase II study, Daisy PETAL

or NBI-56418–0901 study. Furthermore, compared with Liliac PETAL or NBI-56418–0702 study, Daisy PETAL or NBI-56418–0901 study used enhanced baseline criteria for nonmenstrual pelvic pain. In this study, 137 patients with laparoscopically proven endometriosis and moderate-to-severe dysmenorrhea and nonmenstrual pelvic pain, were randomized into elagolix 150 mg q.d. versus placebo for 8 weeks, following which all participants were given elagolix 150 mg q.d. in an open label period for an additional 16 weeks [73]. Primary end points were daily assessment of dysmenorrhea, dyspareunia and nonmenstrual pelvic pain with a modified Biberoglu-Behrman scale using an e-diary. Additional efficacy measures included daily use of analgesics, monthly assessment of CPSSS at baseline, week 8 and week 24, EHP-5 and PGIC. At the end of the 8-week double blind period, there were statistically significant improvements in dysmenorrhea, nonmenstrual pelvic pain and dyspareunia compared with the placebo. Following completion of the active phase of the study, after the 16-week open label period with all participants receiving elagolix, those initially randomized to elagolix and those initially randomized to placebo had a similar reduction in daily pain scores for dysmenorrhea, dyspareunia and nonmenstrual pelvic pain. Similarly, statistically significant improvements were observed in monthly CPSSS scores, analgesic use, EHP-5 and PGIC scores in the group receiving elagolix 150 mg q.d. compared with the placebo group at the end of the 8-week double-blind period, with the difference between the two groups dissipating after the 16-week open-label period [73].

Safety & tolerability

In general, elagolix has had an acceptable safety and tolerability profile, is well tolerated in clinical trials to date and the incidences of overall side effects have been similar between elagolix and placebo groups. The most common side effects among elagolix users (150 mg q.d.) were hot flushes (10.3%), nausea (7.4%) and headache (5.9%). Upon continued use for 6 months, the incidence of each of these side effects increased to about 10%. Elagolix use results in a significant reduction in the number of days with any vaginal bleeding from 23% at screening to 14% after 8 weeks. About 25% of patients on elagolix (150 mg q.d.) developed amenorrhea during the 8-week period, but this number decreased to 7.6% after 24 weeks [73]. Several pregnancies have been reported in elagolix trials and a review of all the data from the early clinical development program of elagolix to date estimates an annualized pregnancy rate of approximately 5% for the 150 mg q.d. dose [74]. The occurrence of these pregnancies is probably explained by the fact that the degree of ovarian suppression with elagolix is dose dependent and not as profound as it is with other GnRH analogs and plausibly the administered dose of elagolix was not adequate to fully suppress the ovarian function in these patients and therefore ovulation and subsequently pregnancy ensued. Two pregnancies have resulted in delivery of healthy infants at term. One pregnancy resulted in a spontaneous miscarriage and one resulted in delivery of an infant with a tracheoesophageal fistula, with neither of these adverse outcomes attributed to elagolix by the investigators, and one of the pregnancy outcomes was a cleft palate [74]. Preclinical studies with elagolix have revealed no teratogenic effects at all doses studied (30–98× the clinically relevant dose). An extensive review (e.g., timing of elagolix exposure relative to organogenesis, absence of teratogenic findings in animal toxicological studies and background incidence of this abnormality, among others) of this congenital abnormality suggests that it is unlikely to be related to elagolix; however, the true relationship remains unknown [74]. With regard to the effects on BMD, elagolix causes a small, but significant reduction in BMD at the spine after 12 weeks, and at spine and femur after 24 weeks [67,74].

Regulatory affairs

Elagolix is currently undergoing two Phase III trials, sponsored by Abbvie Pharmaceutical, Inc. The first one, Violet PETAL (M12–665) started in 2012 with estimated completion date in 2015. This study aims to recruit 875 patients in 160 clinical sites in the USA, Canada and Puerto Rico, comparing the effects of two different elagolix regimens and placebo for a treatment period of 6 months. The second ongoing Phase III trial, Solstice (M12–671), started in 2013 and is similar in design to Violet PETAL. It aims to recruit 788 women in 200 sites globally with an estimated completion date in 2016. The manufacturers are hoping to file their new drug application with FDA in 2016 [54].

Conclusion

Based on the available published data, it appears that orally bioavailable GnRH antagonists in general, and elagolix in particular, have the potential to represent a novel therapeutic option for endometriosis. Their ease of administration, ability to fine-tune the extent of ovarian suppression, lack of serious side effects such as significant reduction in BMD and relatively low incidence of hot flushes make them an appealing choice for long-term use in the treatment of endometriosis-related pain. While the results of Phase III

trials on elagolix are eagerly awaited, other orally bioavailable GnRH antagonists such as TAK-385 may prove to be an additional member of this class of medications.

Disclaimer

AbbVie was asked to review the manuscript for factual accuracy of the safety and efficacy data disclosed herein, all of which is in the public domain. The content and opinion expressed in the manuscript is solely that of the authors.

Financial & competing interests disclosure

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Executive summary

Mechanism of action

- Elagolix is a small molecule, nonpeptide, competitive GnRH receptor antagonist.

Pharmacodynamics

- Elagolix causes a rapid, dose-dependent suppression of pituitary gonadotropins, mainly LH and to a lesser extent FSH, reaching its peak effects 4–6 h after oral administration.
- Elagolix causes a partial, dose-dependent suppression of ovarian estrogen production through inhibition of follicular development.
- In most patients, at the target dose of 150 mg once daily, elagolix causes a partial suppression of estrogen production.

Pharmacokinetics & metabolism

- Following oral administration, elagolix is rapidly absorbed, reaching peak plasma concentration within 30–60 min.
- Elagolix is extensively metabolized and only 3% of the administered dose is excreted intact in the urine.

Clinical efficacy

- Several Phase II clinical trials have demonstrated efficacy of elagolix for the treatment of endometriosis-related dysmenorrhea.
- Newer trials, also have shown its efficacy for the treatment of dyspareunia and nonmenstrual pelvic pain with overall improvement in quality of life based on Endometriosis Health Profile and Patient Global Impression of Change scores.

Safety & tolerability

- Elagolix is well tolerated in the administered dosing range of 50–200 mg taken orally daily.
- The most commonly reported side effects are nausea, headache and hot flushes, each occurring in about 10% of users.
- The adverse effects of elagolix on bone mineral density are mild to minimal.

Regulatory affairs

- Elagolix is currently undergoing two Phase III clinical trials with expected completion dates in 2015 and 2016.

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