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Efficacy of elagolix in the treatment of endometriosis

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Abstract

Introduction: Much research has gone into developing medications that can be used to alleviate endometriosis-associated symptoms. In addition to already established medications, a new GnRH antagonist, elagolix, is in development. The novelty of this drug compared to other GnRH antagonists, is its nonpeptide structure, allowing it to be administered orally.

Areas covered: We analyzed several Phase I, II and III clinical trials that have evaluated the safety and efficacy of this new medication.

Expert opinion: Since many medications have been put on the market and have gained popularity for the treatment of endometriosis-associated symptoms, the demonstration of equality or superiority of effect, tolerability, as well as patient compliance should be assessed when introducing a new drug. While elagolix may have an advantage over established GnRH agonists, in that it does not lead to a 'flare-up' effect, it too, takes a toll on bone mineral density. Nevertheless, studies have shown that this new oral GnRH antagonist is well tolerated, and the side effects have been described as 'mild or moderate'. However, in order to examine whether elagolix can compete with or even surpass established gold-standard medical treatments in this field, further studies that directly compare elagolix to said treatments, might be necessary.

Key words: elagolix, GnRH antagonist, endometriosis, medical therapy

List of abbreviations:

NSAID: nonsteroidal anti-inflammatory drug

COC: combined oral contraceptive

GnRH: Gonadotropin-releasing hormone

LH: luteinizing hormone

FSH: follicle stimulating hormone

MPA: Medroxyprogesterone Acetate

CYP 3A4: Cytochrome P 3A4

E2: Estradiol

EHP: endometriosis health profile

DMPA-SC: subcutaneous depot medroxyprogesterone acetate

NMPP: nonmenstrual pelvic pain

BMD: bone mineral density

AE: adverse event

1. Introduction

1.1. Endometriosis

With an incidence of 6 to 10% in the female population, endometriosis is a frequently encountered gynecological disease, usually diagnosed at the peak of the reproductive age (1). The wide range of symptoms observed in patients with endometriosis is due to implantation of endometrial tissue outside the uterine cavity. This ectopic endometrium is subjected to cyclic changes similar to that of eutopic endometrium. Typically, ectopic lesions are found in the pelvis, notably on the ovaries in the form of cysts, as well as the rectouterine and vesicouterine pouch. Lesions have also been described in other parts of the abdomen and in other locations outside the abdominal cavity (2–4).

Although endometriosis has also been described in asymptomatic patients, possible symptoms range from mild to severe pain presenting itself as dysmenorrhea, dyspareunia, or dyschezia, or as infertility. The most severe symptoms are found in cases of deep infiltrating endometriosis, characterized by a penetration of at least 5mm into the affected tissue (5). Due to these symptoms, this disorder reduces not only quality of life, but also takes a psychological toll on patients, reportedly causing depression and anxiety disorders (6).

Since the clinical picture varies, the treatment of this disease has become quite personalized. Many studies conducted over the past several years have presented different treatment options for the symptoms caused by endometriosis.

1.2. Currently established treatments

1.2.1. NSAID and COC

Often prescribed as the first line therapy for the relief of symptoms such as dysmenorrhea, is a combination of a nonsteroidal anti-inflammatory drug (NSAID) and continuous hormonal contraceptives. Although the clear benefit of NSAID in these cases, when considering the large range of possible side effects, remains unclear (7), significant pain relief has been described (8). Oral contraceptives with a combination of estrogens and progestins (COC) have several favorable effects that contribute to the treatment of symptoms. It has been reported that this group of medications lowers the risk of endometrioma formation by inhibiting ovulation, downregulates endometrial cell proliferation and possibly induces apoptosis of ectopic endometrium. Furthermore, estrogen-progestin contraceptives have been shown to have limited side effects despite continuous intake, and to reduce the risk of ovarian, endometrial, and colon cancer (9).

1.2.2. Progestins

An alternative to combined oral contraceptives is progestin-only therapy. The most prescribed medications of this group are Medroxyprogesterone Acetate (MPA), administered intramuscularly every three months as a depot, Norethindrone Acetate, administered orally in a starting dose of 5 mg, increasing up to 15 mg per day, as well as Dienogest (2 mg). The effect mechanism of these drugs is similar to the mechanism of COC, preventing endometrial tissue growth, and thus, leading to decidualization and atrophy (10). While the adverse effects of progestins include loss of bone density, weight gain, depression, and breakthrough bleeding (11), treatment with progestins does not increase the risk of thromboembolic events, as opposed to the use of estrogen-progestin contraceptives.

1.2.3. Danazol

Danazol, a synthetic androgen, and a derivate of 17α-ethynyl testosterone, has moved into the background when searching for symptom-relief medication in patients with endometriosis, due to its large range of side effects such as weight gain, acne, seborrhea, and vaginal atrophy (12).

1.2.4. GnRH agonists

The main role in the regulation of hormone secretion in women is played by the hypothalamic-hypophyseal-ovarian axis. By stimulating the receptor of the Gonadotropin-releasing hormone (GnRH) located in the pituary gland, GnRH, produced by neurons situated in the hypothalamus, activates the production of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which, in turn, trigger the ovarian production of estrogen and progesterone (13). The GnRH receptor, therefore, soon became a target for treatments that aimed to decrease ovarian hormone production. The first medications of this sort to flood the market were GnRH agonists, such as Nafarelin, Leuprolide, Goserelin, Buserelin and Triptorelin. These synthetically produced agonists have a structure similar to that of endogenous GnRH, but a longer half-life. They take effect by leading to a down-regulation of GnRH-receptors, preceded by a short stimulation surge, referred to as the "flare-up effect" (14). This down-regulation leads to hypoestrogenism, and, consequently, to amenorrhea and endometrial atrophy. The hypoestrogenic state is also the cause of the adverse effects attributed to this medication, such as vaginal dryness, hot flashes, reduced libido, decrease of bone density, and mood swings. These side effects can be minimized by combining GnRH agonist therapy with progestins (norethindrone acetate, in particular) or with estrogen-progestin contraceptives. This so called "add-back therapy" also allows for longer administration of this medication (10). GnRH agonists have not shown superiority in the

treatment of endometriosis-associated pain compared to other established hormonal therapies (15,16).

1.2.5. GnRH antagonists

GnRH antagonists act by competing for and blocking the GnRH receptor, thus leading to a more rapid suppression of hormone production in the pituitary gland, and thus, avoiding the flare-up effect (13). Several recent studies have examined the efficacy of these medications in the treatment of endometriosis-associated symptoms. Belonging to this group of medications is the drug 'elagolix,' or '*R-4-{2-[5-(2fluoro-3-methoxyphenyl)-3-(2-fluoro-6-[trifluoromethyl]benzyl)4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1phenylethylamino}butyrate*'(17).

2. Methods

The research was conducted through a literature acquired after entering the search terms "elagolix-Endometriosis" in PubMed, as well as working with a list of references provided by the company AbbVie.

3. Elagolix

3.1. Drug Chemistry

NBI-42902, the predecessor compound of elagolix, was found to be a potent oral GnRH receptor antagonist in in vitro studies, and was shown to suppress LH production in castrated macaques and postmenopausal women (17). However, this compound also showed a high

affinity for the Cytochrome P 3A4 (CYP 3A4) receptor, which increased its risk for drug-drug interactions, as CYP 3A4 plays a main role in the metabolism of many medications. After a series of molecular transformations, notably creating a butyrate as well as incorporating a carboxylic group, manufacturers managed to retain its predecessor's high affinity to the GnRH receptor, as well as to reduce its effect on in the CYP 3A4 receptor. (17) While most GnRH antagonists currently on the market can be administered only through injection because of their peptide structure, elagolix, as a nonpeptide, can be administered orally.

3.2. Pharmacodynamics

A Phase I randomized, double blind, placebo-controlled, sequential dose escalation study compared nine cohorts with each other, each cohort being administered a different dose of elagolix. In the single-dose cohort, it could be shown that a rapid blockage of the GnRH receptor could be achieved, followed by a significant decrease of LH and FSH. LH was measured at a concentration of 22-35% of baseline concentration, four hours after drug administration, slowly recovering after 4-6 hours, with a prolonged suppression observed in cohorts that received higher doses. After 24 hours, a return to baseline concentrations was observed in all groups, correlating with the elimination of elagolix from the system. To a lesser extent, a suppression of FSH was also noted. FSH levels reached 62-71% of baseline concentration after 8-10 hours. Furthermore, a dose-dependent suppression of E2 was observed. Similar results were found in the multiple dose cohorts. (18)

3.3. Pharmacokintetics and metabolism

Pharmacokinetics were analyzed by the two Phase I clinical studies. T_{max} was shown to be reached after 0.5 to 1 hour (18), and 1 to 1,5 hours (14) respectively, with the drug being

absorbed shortly after oral intake, while mean plasma $t_{1/2}$ ranges from 2.4 – 6.3 hours. Furthermore, a low renal clearance has been noted, with only 3% of the administered dose being excreted through urine (18).

3.4. Clinical efficacy

3.4.1. Phase I clinical studies

The overview of Phase I clinical studies regarding elagolix is displayed in Table 1.

Five of the nine cohorts in this Phase I clinical study received one single dose of elagolix 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, or placebo. Once the safety of the medication was established in these cohorts, three cohorts that received 50 mg, 100 mg, 200 mg, or placebo daily for seven days and one that received elagolix 100 mg twice daily or placebo, were enrolled. The first dose of elagolix was administered on day 7 $\pm$ 1 after the onset of menstruation. As previously mentioned, a suppression of LH and FSH could be achieved in all groups, whereas a dose dependent suppression of E2 was noted. While the E2 concentration was lowered to 42-65% of baseline concentration at 24 hours in the cohorts that received 50 mg, 200 mg, or 400 mg, no significant suppression was measured in the 100 mg group, and no difference from the placebo group was noted in the 25mg group. Similar results were described in the multiple-dose cohorts: LH concentration reached its lowest levels at 4-6 hours, and, except for the 100 mg cohort in which LH concentrations remained suppressed after 24 hours, then returned to baseline concentrations. The same could be said for FSH concentrations. Finally, a suppression of E2 on the first day after drug administration was noted in all groups (18).

Another phase I clinical study compared elagolix 150 mg once daily, as well as elagolix 100 mg, 200 mg, 300 mg, and 400 mg twice daily to a placebo, with regard to hormone response,

safety, and pharmacokinetics. Medication intake was started two days after the onset of menstruation. The results were similar to previous studies: A dose-dependent suppression of estrogen (E2), progesterone, LH, and FSH was observed, the suppression of FSH being the most efficient with elagolix 300 mg and 400 mg, while the clearest decrease in LH and E2 was found with elagolix 200 mg. The concentration of progesterone remained at unovulatory levels throughout the study period at the lowest dose of elagolix. (14).

3.4.2. Phase II clinical studies

The overview of Phase II clinical studies regarding elagolix is displayed in Table 2.
A phase II clinical study, conducted by Diamond et al. (19), examined the effect of elagolix vs placebo on dysmenorrhea and nonmenstrual pelvic pain in women with endometriosis. The first stage of the study lasted 12 weeks and compared three groups with one another: a control group (i.e., placebo); a group of patients receiving 150 mg elagolix; and a third group receiving 250 mg. At the end of these first 12 weeks, endometriosis-associated pain had decreased in all three groups. A correlation could be found between the subjective amount of pain decrease and the dose of the medication. After 12 weeks, the patients of the placebo-group were reallocated to one of the groups receiving elagolix. In this second stage, there was a further reduction of dysmenorrhea in both groups. Similar results were achieved for dyspareunia. Statistical significance was seen here between elagolix 150 mg and placebo during weeks 8 to 12, as well as between elagolix 250 mg and placebo during weeks 4 to 8. Furthermore, a decrease in the use of prescription analgetics was seen in the elagolix groups, while the biggest improvement in quality of life, assessed using the endometriosis health profile (EHP), was noted specifically in the elagolix 150mg group.

Similar results were described in the phase II clinical trial conducted by Carr et al. (20). The

effect of 150 mg elagolix was compared to placebo over an eight-week, double-blind, placebo- controlled treatment period, followed by a 16-week open-label treatment period, during which all patients received elagolix 150 mg once daily. During these first eight weeks, there was a significant reduction from baseline for dysmenorrhea, dyspareunia, and nonmenstrual pelvic pain, measured using a four-point modified Biberoglu-Behrman scale. This observation expanded to both groups during the open-label treatment period. However, when evaluated six weeks after treatment, it was noted that the mean reductions in these parameters were less, compared to the treatment period. The use of mild and strong analgetics was permitted in this study; however, only 'as-needed,' and not in the form of prophylactic use. Here too, differences between the two groups were observed during the first eight weeks: a significant reduction in the use of such analgetics was noted in the group receiving elagolix 150mg, compared to the group receiving the placebo, as well as in both groups during the following 16 weeks. Furthermore, a significant improvement in quality of life, represented by the factors 'pain,' 'control and powerlessness', 'self-image,' and 'social support' (i.e., four of the five factors included on the EHP), was observed in the elagolix group during the eight-week treatment period, and in both groups during the open-label treatment period. Finally, it should be noted, that, even though the patients included in the study were required to use a combination of two barrier methods, five pregnancies occurred during the study period. Of the three pregnancies that occurred during the actual treatment period, two were found in women being treated with the medication, and resulted in the delivery of healthy, full-term infants, while one pregnancy seen in a patient included in the placebo group resulted in a spontaneous abortion. Of the two pregnancies that occurred after treatment (both in women who had been included in the elagolix group), one resulted in a spontaneous abortion, while the second infant was healthy and was carried to full-term, respectively.

Due to their hypoestrogenic effect, GnRH agonists and antagonists have been shown to cause a loss of bone mineral density. This is one of the reasons long-term treatment with GnRH agonists is limited. Carr et al. (21) compared the extent of this side effect in patients receiving elagolix 150 mg once daily or 75 mg twice daily, with patients who received subcutaneous depot medroxyprogesterone acetate (DMPA-SC), a medication frequently used in the treatment of endometriosis-associated symptoms and known to cause a loss of bone mineral density. These authors also compared the efficacy of these medications for endometriosis-associated pain. All three groups showed a significant reduction in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia. Mean estradiol changes from baseline, however, were not significant: starting from baseline levels of 41.1 pg/ml, 39.1 pg/ml, and 39.3 pg/mL in the elagolix 150 mg, 200 mg, and DMPA-SC groups, respectively, Levels during the treatment period ranged from 36 to 63 pg/ml, from 23 to 31 pg/ml, and from 19 to 37 pg/ml in the three study groups. While the incidence of adverse events was similar in all three groups, it was observed that more women from the DMPA-SC group discontinued the medication due to these events (notably due to menorrhagia), compared to the elagolix groups. The most common adverse events in the elagolix groups were nausea, headaches, and nasopharyngitis, while the most common in the DMPA-SC cohort were headache, nausea, and mood swings. The occurrence of hot flashes was comparable in all groups. Finally, it was noted that both elagolix and DMPA-SC had similar minimal effects on bone mineral density. elagolix 75 mg twice daily led to an increased suppression of estrogen production. Consequently, a larger effect on bone mineral density was observed when compared to 150 mg once a day. Due to this, it was postulated that 150 mg once daily might be a more suitable dose for longer-term treatment, without the need for add-back therapy.

3.4.3. Phase III clinical studies

The overview of Phase III clinical studies regarding elagolix is displayed in Table 3.

In May 2017, the results from two multicenter, double blind, randomized, placebo-controlled, phase III trials (Elaris Endometriosis I and II) were published (22). The patients enrolled in both studies were premenopausal women between the ages of 18 and 49, who had surgically diagnosed endometriosis and suffered from moderate to severe endometriosis-associated pain. Elaris EM I (22) was conducted in the United States and Canada between 2012 and 2014. There were 872 women included, and 653 (74.9%) completed the six-month study period. Elaris EM II took place in thirteen countries, including the United States. Of the 817 women enrolled, 632 (77.4%) completed the trial. Both trials consisted of a ‘washout period of hormonal therapy,’ if applicable, and a ‘screening period,’ during which the patients changed from their usual analgetic medication to one of the few analgetics permitted in the study, followed by a six-month treatment period. The patients were then enrolled in either the six-month extension study or included in the 12-month follow-up period. The primary endpoints of both studies were efficacy, with regard to alleviation of dysmenorrhea and nonmenstrual pelvic pain (NMPP), after three months of elagolix 150 mg once daily or elagolix 200 mg twice daily, compared to placebo, measured in a reduced pain score and reduced intake of rescue analgetics. Safety was evaluated through the measurement of bone mineral density, endometrial assessments, and laboratory measures. In the Elaris EM I study, after three months of treatment, 46.4% of the women treated with elagolix 150 mg, and 75.8% of the patients treated with elagolix 200 mg daily, vs 19.6% of the women in the placebo group, were noted to be 'dysmenorrhea responders,' while 50.4% of the women treated with elagolix 150 mg and 54.5% of the women treated with 200 mg elagolix vs 36.5% of the women in the placebo group, were described as 'NMPP responders.' Similar results were found in the Elaris EM II trial for the 150 mg group, the 200 mg group, and the placebo

group, with 43.4% and 72.4% vs 22.7%, respectively, of women who described a reduction of dysmenorrhea and 49.8% and 57.8% vs 36.5%, respectively, of women who described a reduction of nonmenstrual pelvic pain, as well as a decrease in intake of analgetics. These results were all found to be statistically significant. After three and six months, the difference in intake of rescue analgetics between the elagolix 150 mg group and the placebo group was not found to be significant, while the contrary was noted in the group of women who received the higher dose compared to the placebo. Furthermore, a significant improvement in quality of life, measured using the Endometrioses Health Profile dimensions, was noted in the elagolix-treated groups.

3.5. Safety and tolerability

Similar adverse events were described throughout all clinical trials.

The Phase I clinical trials noted nausea and hot flashes as the most common adverse events (AE), being described as mild to moderate in severity. Ng et al observed, that the highest incidence of hot flashes occurred in women receiving an elagolix dose of at least 200mg twice daily. Furthermore, spotting was reported by 7 of the patients included in this study. However, these AEs did not lead to a discontinuation of study participation. Finally, no changes or differences from the placebo group were found with regard to electrocardiograms, blood tests, or vital signs (14). Struthers et al described headaches and nausea in the single-dose-, nausea, hot flashes, and abdominal pain in the multiple-dose cohorts as the most frequent AEs. Here too, these effects were described as mild to moderate.

The most common adverse events described by Carr et al (20) in the Phase II clinical study included headache, nausea, and hot flashes. The incidence of these adverse events was found

to be similar in both groups. Diamond et al (19) described an increased occurrence of headache, nausea, and anxiety. 4 patients dropped out of the study due to one of these more frequently observed AEs. Furthermore, a significant decrease in bone-mineral density was noted here in both the elagolix 150mg and elagolix 250mg groups.

Finally, more than 70% of women in both Phase III trials noted the occurrence of adverse events, which was significantly higher in the elagolix 200mg group compared to the placebo group. These events, described as mild or moderate, were similar to previously performed studies, the most common being hot flashes, headaches, and nausea. When examining the effect of elagolix on bone mineral density, a significant dose-dependent decrease of lumbar BMD was noted after six months of treatment in both groups. Laboratory results showed an elagolix-associated increase in low-density and high-density lipoprotein cholesterol, as well as triglycerides. Finally, as has been described in previous studies, despite dual nonhormonal contraception, 23 pregnancies occurred during the trial period. However, no deduction could be made regarding the effect of the medication on pregnancy outcome.

4. Regulatory affairs

A FDA New Drug Application for elagolix as treatment for endometriosis is set to be submitted for approval by AbbVie in the course of the year 2017.

5. Conclusion

The Phase I clinical studies that evaluated pharmacokinetics, effect on hormone concentration, and tolerability, observed a significant dose-dependent suppression of LH,

FSH, and E2, while progesterone concentrations remained at unovulatory levels throughout the study period. Adverse events noted in the elagolix cohorts included headache, nausea and hot flashes. Next to these adverse events, Phase II clinical studies also observed a decrease of bone mineral density, comparable with the effect of other established medications. Furthermore, in addition to tolerability, these studies also evaluated the efficacy in reduction of dysmenorrhea and NMPP. It was noted, that the intake of elagolix lead to a significant reduction of dysmenorrhea and nonmenstrual pelvic pain and, consequently, to a reduced intake of rescue analgetics. However, these studies also observed a decrease of bone mineral density in patients The two multinational Phase III clinical studies led to the same conclusion: a significant reduction of dysmenorrhea and NMPP as well as an improvement in quality of life was observed, while the side effects, which included headache, nausea and hot flashes, were, in most cases, tolerated. Based on existing publications however, we cannot make a definitive statement about the correlation between E2 values and efficacy of the medication regarding symptom alleviation.

6. Expert opinion

Pharmacotherapy plays a critical role in the treatment of endometriosis. Due to its varied clinical presentations, many different pharmaceutical treatment options have been established. Since most of these medications are put in use to achieve similar goals—notably a decrease in ovarian estrogen production leading to the inhibition of ectopic endometrial growth—a key factor in choosing the medication is the spectrum of side effects, as well as possible patient compliance. When examining established GnRH agonist or antagonist treatments, agonists seem to have the disadvantage of the flare-up effect, while GnRH antagonists lead to an immediate blockage of the GnRH receptor, without initial stimulation.

In contrast to other GnRH antagonists currently on the market, elagolix, as a nonpeptide, is administered orally. This avoids the side effects seen with intramuscular injection, such as pain, redness, numbness or general discomfort at the injection site. However, by administering medications via injection, the correct intake of this medication can be controlled by the healthcare worker who provides the injection. When prescribing pills to be taken orally, however, we must rely on patient-compliance, which, when faced with having to ingest a pill on a regular basis, could be reduced. In order for a new medication such as elagolix to become the gold standard in the medical treatment of endometriosis-associated symptoms, its superiority or, at least, its non-inferiority compared to well-established pharmacological treatment methods, has to be demonstrated. The two pivotal Phase III studies show, that elagolix achieves its primary endpoints, notably a reduction in endometriosis-associated pain, while adverse events were described as mild to moderate. However, the hypoestrogenic effect of the medication, shown through a reduction in bone mineral density and an increase in lipid measurements, seems to be comparable to the effect of GnRH agonists, which have not been shown to be superior to other established hormonal treatments in the field of endometriosis-associated pain (15,16). Further studies might be necessary in order to directly compare the effect, tolerability, and patient-compliance of elagolix vs current, frequently used medications, such as progestins, COC, GnRH agonists, or intramuscularly administered GnRH antagonists, for example, to evaluate the necessity of add-back therapy in prolonged administration, as well as to study the effects of the drug on ovarian function, in particular ovulation, as several pregnancies were descried during intake of elagolix.

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22. Diamond MP, Surrey E, Johnson NP, Watts NB, Gallagher JC, Simon JA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. 2017;** This is a multinational Phase III clinical trial that further evaluates elagolix as a potent medical treatment for endometriosis.

Table 1: Overview of Phase I clinical studies

Authors (reference)	Study design	N (enrolled)	Elagolix dose (in mg) vs Placebo	Primary Endpoints	Outcome
Struthers et al (18)	randomized, double-blind, placebo-controlled, sequential dose escalation study	55	25, 50, 100, 200, 400 single dose or 50, 100, 200 1x/d or 100 2x/d	hormone concentrations pharmacokinetics safety - adverse events	decrease of LH, FSH decrease of E2 in 50, 200, 400mg group Tmax 0,5-1h, T1/2 2,4-6,3h headaches, nausea, hot flash
Ng et al (14)	randomized, double-blind, placebo-controlled, sequential dose- escalation study	45	150 1x/d 100,200,300,400 2x/d	hormone concentration pharmacokinetics adverse events	dose-dependent supression of LH, FSH, E2 Progesterone at unovulatory levels Tmax 0,5-1h, T1/2 4-6h hot flash, headache

Table 2: Overview of Phase II clinical studies

Authors (reference)	Study design	N (enrolled)	Elagolix dose (in mg)	Primary Endpoints	Outcome
Diamond et al (19)	randomized, multicenter, double-blind placebo-controlled, parallel group study	155	150, 250 1x/d vs. placebo	efficacy	NMPP (Biberoglu and Behrman scale): sign. reduction Dysmenorrhea: sign. reduction Dyspareunia: sign. Reduction
				quality of life	greatest improvement in Elagolix 150mg group
				safety - adverse events	headache, nausea, anxiety
Carr et al (20)	randomized, placebo-controlled parallel group study	137	150 1x/d vs. placebo	efficacy	NMPP: sign. reduction Dysmenorrhea: sign. reduction Dyspareunia: sign. Reduction
				quality of life	significant improvement
				safety - adverse events	headache, nausea, hot flash
Carr et al (21)	randomized, multicenter, double-blind, and active-controlled study	252	150 1x/d 75 2x/d	effect on BMD	similar minimal effects in all groups (largest effect seen in Elagolic

					75mg 2x/d group)
			vs. DMPA-SC 104 mg/0.65 mL	effect on E2-concentration	no significant decrease from basline in all groups
				efficacy	NMPP: sign. reduction in all 3 groups Dysmenorrhea: sign. reduction in all 3 groups Dyspareunia: sign. Reduction in all 3 groups
				safety-adverse events	Elagolix: nausea, headache, nasopharyngitis, hot flash DMPA-SC: headache, nausea, mood swings, hot flash

Table 3: Overview of Phase III clinical studies

Authors (reference)	Study design of both trials	N (enrolled)	Elagolix dose (in mg) in both trials	Primary Endpoints in both trials	Outcome in both trials
Taylor et al (22)	multicenter, double blind, randomized, placebo-controlled trial	Elaris EM I/ Elaris EM II 872 / 817	150 1x/d 200 2x/d vs. placebo	efficacy	NMPP: sign. reduction in both Elagolix groups Dysmenorrhea: sign. reduction in both Elagolix groups use of rescue analgetics: sign. reduction in both Elagolix groups
				quality of life	significant improvement in both

					Elagolix groups
				safety-adverse events	hot flasch, headache, nausea
				effect on BMD	significant decrease in both Elagolix groups

Drug name	Elagolix
Phase	I, II, III
Indication (specific to discussion)	Endometriosis
Pharmacology	GnRH antagonist
Route of administration	oral
Chemical structure	R-4-{2-[5-(2fluoro-3-methoxyphenyl)-3-(2-fluoro-6-[trifluoromethyl]benzyl)4 methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1phenylethylamino}butyrate
Pivotal trials	Elaris EM I, Elaris EM II

Table 4 Drug summary