

АО «Медицинский университет Астана»

**Доказательная медицина в моей  
специальности.**

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Группа: АиГ 121

Астана 2019

# Введение

- Эндометриоз – хроническое рецидивирующее заболевание репродуктивных и нерепродуктивных органов женщин, которая характеризуется болевыми синдромами (дисменорея, диспареуния, дизурия, дисхезия, боли в пояснице или внизу живота, хроническая тазовая боль), бесплодием, нарушением менструальной функции.
- На сегодняшний день, по данным ВОЗ, около 200 миллионов женщин в мире страдают этой патологией. Отмечается рост этого заболевания в последние десятилетия, о чем свидетельствует большое число публикаций.
- По опубликованным данным Международного Центра Эндометриоза в Казахстане эндометриоз наблюдается у **757 185** женщин, что составляет **17%** ко всем женщинам репродуктивного возраста. Значит каждая **6** женщина детородного возраста в нашей стране страдает эндометриозом

# Актуальность

- Несмотря на то, что прошло более 150 лет, как эта патология была обозначена нозологической единицей, до настоящего времени не до конца решены вопросы патогенеза, диагностики эндометриоза. Особенно актуальна в настоящее время **проблема лечения эндометриоза**. Отмечается высокий рецидив заболевания и неэффективность терапии.

# Вопрос

- Р- женщины с эндометриозом
- I- назначение антагонистов ГнРГ
- С- не назначение антагонистов ГнРГ
- О- эффективность лечения

**Эффективно ли назначение антагонистов ГнРГ  
в отношении лечения женщин с эндометриозом?**

# Ключевые слова, которые были мною использованы, во время поиска нужного материала:

- Endometriosis
- Elagolix
- Endometriosis treatment;
- GnRH antagonist
- Pharmacokinetics of Elagolix
- Dysmenorrhea
- hormonal contraception
- pelvic pain
- gonadotropin-releasing hormone
- Medical treatment
- Dienogest



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**Elagolix** sodium (Orilissa) - For the management of moderate to severe pain associated with **endometriosis** Drug Approval Package: Orilissa (**elagolix** sodium) U.S. Department of Health and Human Services Search FDA Submit search Drug Approval Package: Orilissa (**elagolix** sodium) Company: AbbVie Inc. Application Number: 210450 Approval Date: 07/23/2018 Persons with disabilities having problems accessing the PDF files below may call (301) 796-3634 for assistance. FDA Approval Letter and Labeling (PDF

2018 FDA - Drug Approval Package

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Best Pract Res Clin Obstet Gynaecol. 2018 Aug;51:92-101. doi: 10.1016/j.bpobgyn.2018.01.021. Epub 2018 Feb 15.

## From pathogenesis to clinical practice: Emerging medical treatments for endometriosis.

Clemenza S<sup>1</sup>, Sorbi F<sup>1</sup>, Noci I<sup>1</sup>, Capezzuoli T<sup>1</sup>, Turrini I<sup>1</sup>, Carriero C<sup>1</sup>, Buffi N<sup>1</sup>, Fambrini M<sup>1</sup>, Petraglia F<sup>2</sup>.

### ⊕ Author information

### Abstract

Endometriosis is a chronic disease, and a lifelong management plan should be developed by using pharmacological treatment and surgical procedures. The pathogenesis of endometriosis is complicated and has not been definitively established. The mechanisms involved are numerous, and their understanding is constantly evolving. Currently, the first-line drugs act by blocking ovarian function, creating an hypoestrogenic environment. The blockade of estrogen secretion and receptor activity and the activation of progesteron receptors are the main target of several current drugs, as well as those under development. The oral GnRH antagonists, the aromatase inhibitors, SERMs, and SPRMs are the hormonal drugs currently studied for treating endometriosis. The increasing knowledge of the pathogenesis has allowed the development of new treatments. The most studied are the anti-inflammatory drugs, starting from the new NSAIDs to the monoclonal antibodies and the statins. Among the antiangiogenic compounds, a role is suggested for Icon, PPARs, and HDACs. A new class of drugs is the cannabinoids. The aim of this review was to investigate the new therapeutic hormonal and non-hormonal alternatives to standard treatments.

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**KEYWORDS:** Antiangiogenic drugs; Aromatase inhibitors; Cannabinoids; Endometriosis; GnRH antagonist; Immunomodulators

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**Review** New medical treatments for endometriosis [Best Pract Res Clin Obstet Gyn...]

**Review** [New medical treatments for painful endometriosis: [Gynecol Obstet Fertil Senol. 2...]

**Review** Current and Emerging Therapeutics for the Management of Endometriosis. [Drugs. 2018]



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N Engl J Med. 2017 Jul 6;377(1):28-40. doi: 10.1056/NEJMoa1700089. Epub 2017 May 19.

## Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist.

Taylor HS<sup>1</sup>, Giudice LC<sup>1</sup>, Lessey BA<sup>1</sup>, Abrao MS<sup>1</sup>, Kotarski J<sup>1</sup>, Archer DF<sup>1</sup>, Diamond MP<sup>1</sup>, Surrey E<sup>1</sup>, Johnson NP<sup>1</sup>, Watts NB<sup>1</sup>, Gallagher JC<sup>1</sup>, Simon JA<sup>1</sup>, Carr BR<sup>1</sup>, Dmowski WP<sup>1</sup>, Leyland N<sup>1</sup>, Rowan JP<sup>1</sup>, Duan WR<sup>1</sup>, Ng J<sup>1</sup>, Schwefel B<sup>1</sup>, Thomas JW<sup>1</sup>, Jain R<sup>1</sup>, Chwalisz K<sup>1</sup>.

### + Author information

### Abstract

**BACKGROUND:** Endometriosis is a chronic, estrogen-dependent condition that causes dysmenorrhea and pelvic pain. Elagolix, an oral, nonpeptide, gonadotropin-releasing hormone (GnRH) antagonist, produced partial to nearly full estrogen suppression in previous studies.

**METHODS:** We performed two similar, double-blind, randomized, 6-month phase 3 trials (Elaris Endometriosis I and II [EM-I and EM-II]) 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 women with surgically diagnosed endometriosis and moderate or severe endometriosis-associated pain. The two primary efficacy end points 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. Each of these end points was measured as a clinically meaningful reduction in the pain score and a decreased or stable use of rescue analgesic agents, as recorded in a daily electronic diary.

**RESULTS:** 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. At 3 months, a significantly greater proportion of women who received each elagolix dose met the clinical response criteria for the two primary end points than did those who received placebo. In Elaris EM-I, the percentage of women who had a clinical response with respect to dysmenorrhea was 46.4% in the lower-dose elagolix group and 75.8% in the higher-dose elagolix group, as compared with 19.6% in the placebo group; in Elaris EM-II, the corresponding percentages were 43.4% and 72.4%, as compared with 22.7% ( $P < 0.001$  for all comparisons). In Elaris EM-I, the percentage of women who had a clinical response with respect to nonmenstrual pelvic pain was 50.4% in the lower-dose elagolix group and 54.5% in the higher-dose elagolix group, as compared with 36.5% in the placebo group ( $P < 0.001$  for all comparisons); in Elaris EM-II, the corresponding percentages were 46.0% and 67.0%, as compared with

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Elagolix, an oral GnRH antagonist, versus subcutaneous depot medroxyprogesterone acetate [Reprod Sci. 2014]

Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, controlled trial [Reprod Sci. 2014]

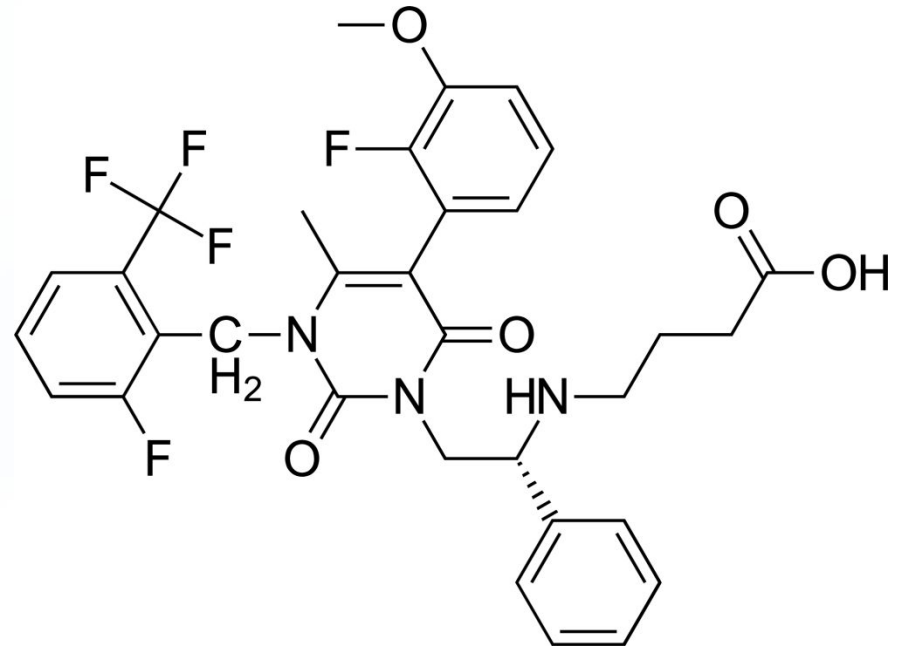
**Review** Elagolix, a novel, orally bioavailable GnRH antagonist [Womens Health (Lond). 2015]

**Review** Efficacy of elagolix in the treatment of endometriosis. [Expert Opin Pharmacother. 2017]

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Elagolix - биодоступный, пероральный, не пептидный антагонист гонадотропин-рилизинг-гормона (GnRH), вызывает частичное или полное подавление эстрогена. Поскольку степень подавления яичников, полученная с помощью elagolix, зависит от дозы, облегчение боли может быть достигнуто путем модуляции уровня гипоэстрогенизма при ограничении побочных эффектов.

# Методы

- Проведено два аналогичных двойных слепых рандомизированных 6-месячных исследования (Эларис эндометриоз I и II [EM-I и EM-II]), чтобы оценить влияние двух доз элаголикса - 150 мг один раз в день (ниже группа дозы) и 200 мг два раза в день (группа с более высокой дозой) - по сравнению с плацебо.



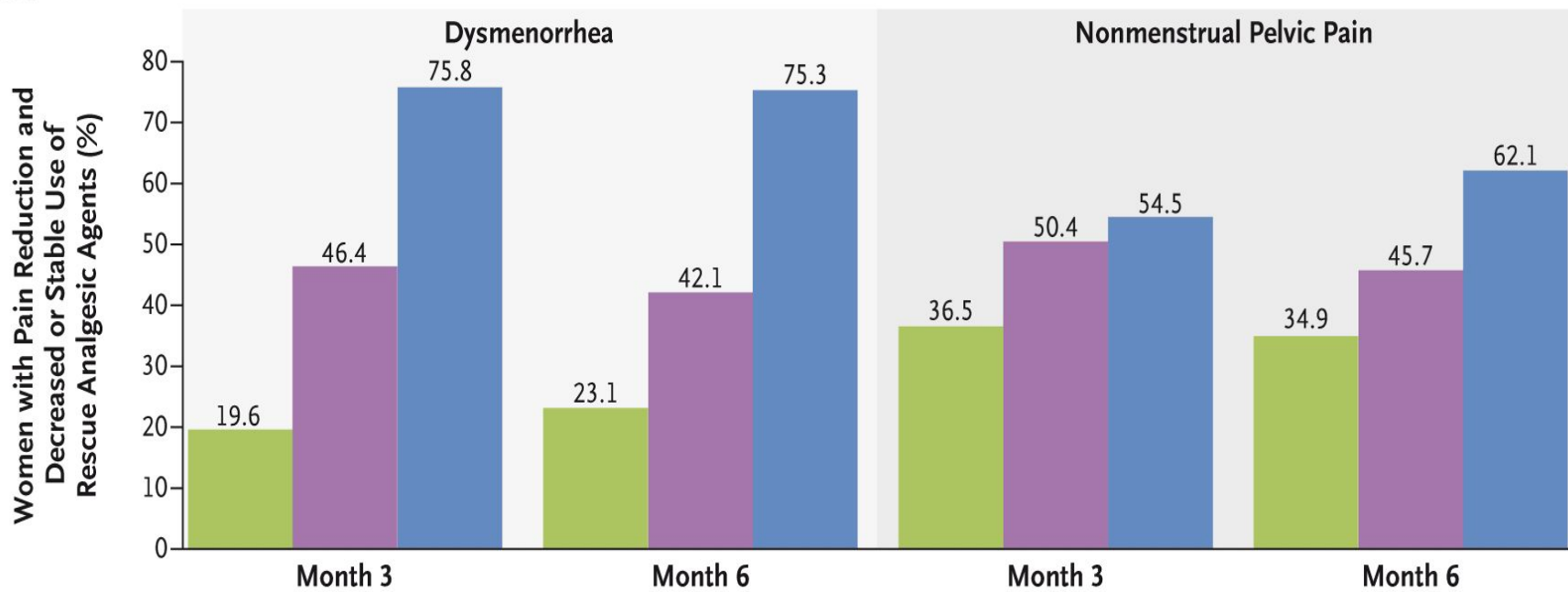


# Результаты

- В общей сложности 872 женщины прошли рандомизацию в Elaris EM-I и 817 в Elaris EM-II; из них 653 (74,9%) и 632 (77,4%) соответственно завершили вмешательство. Через 3 месяца значительно большая доля женщин, получавших каждую дозу элаголикса, соответствовала критериям клинического ответа для двух первичных конечных точек, чем те, кто получал плацебо. В Elaris EM-I процент женщин, у которых был клинический ответ в отношении дисменореи, составлял 46,4% в группе с более низкой дозой элаголикса и 75,8% в группе с более высокой дозой элаголикса группа по сравнению с 19,6% в группе плацебо; в Elaris EM-II соответствующие проценты составили 43,4% и 72,4% по сравнению с 22,7% ( $P < 0,001$  для всех сравнений).

■ Placebo ■ Elagolix, 150 mg once daily ■ Elagolix, 200 mg twice daily

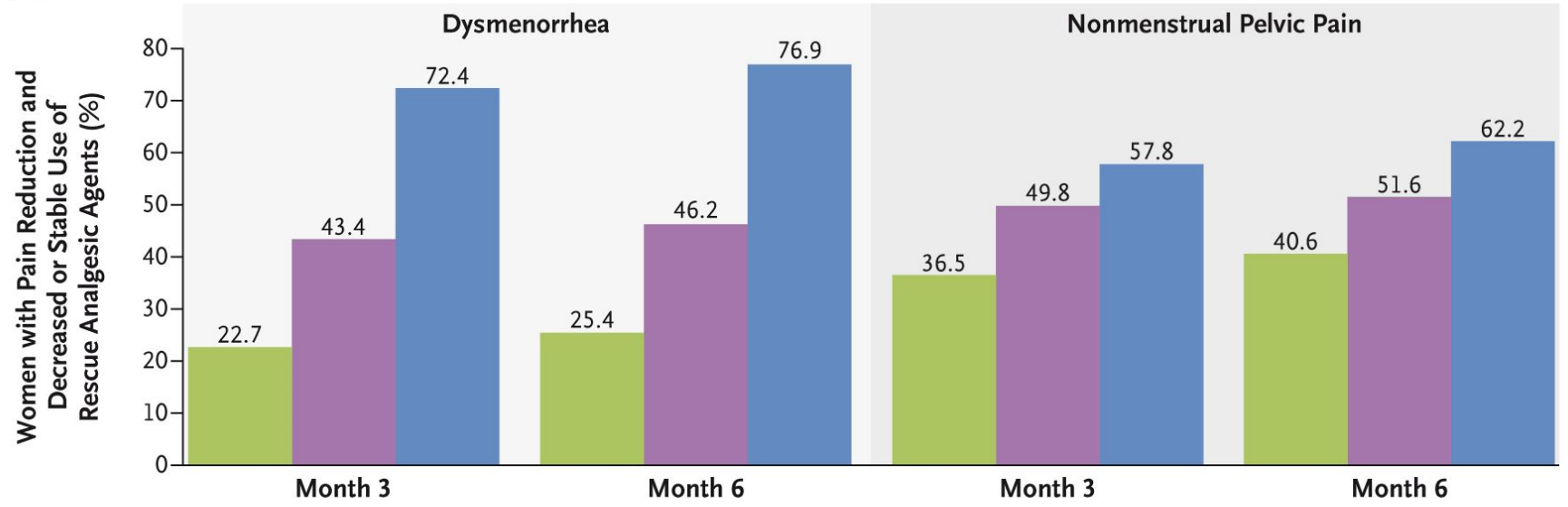
**A Elaris EM-I**



Difference from placebo — % (97.5% CI)	27 (18–35)	56 (49–64)	19 (10–28)	52 (44–60)	14 (5–23)	18 (9–27)	11 (2–20)	27 (18–36)
Risk ratio (97.5% CI)	2.4 (1.7–3.1)	3.9 (2.9–4.9)	1.8 (1.3–2.3)	3.3 (2.5–4.0)	1.4 (1.1–1.7)	1.5 (1.2–1.8)	1.3 (1.0–1.6)	1.8 (1.4–2.1)
Two-sided P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.008	<0.001

- В Elaris EM-I процент женщин, у которых был клинический ответ в отношении неменструальной тазовой боли, составлял 50,4% в группе с более низкой дозой элаголикса и 54,5% в группе с более высокой дозой элаголикса по сравнению с 36,5% в группе плацебо. группа ( $P < 0,001$  для всех сравнений); в Elaris EM-II соответствующие проценты составляли 49,8% и 57,8% по сравнению с 36,5% ( $P = 0,003$  и  $P < 0,001$  соответственно). Ответы в отношении дисменореи и неменструальной боли в области малого таза были устойчивыми через 6 месяцев. Женщины, которые получили elagolix имели более высокую частоту приливов (в основном легкой или умеренной степени), более высокие уровни липидов в сыворотке и большее снижение от базовой линии минеральной плотности кости, чем у тех, кто получал плацебо; не было никаких неблагоприятных результатов эндометрия.

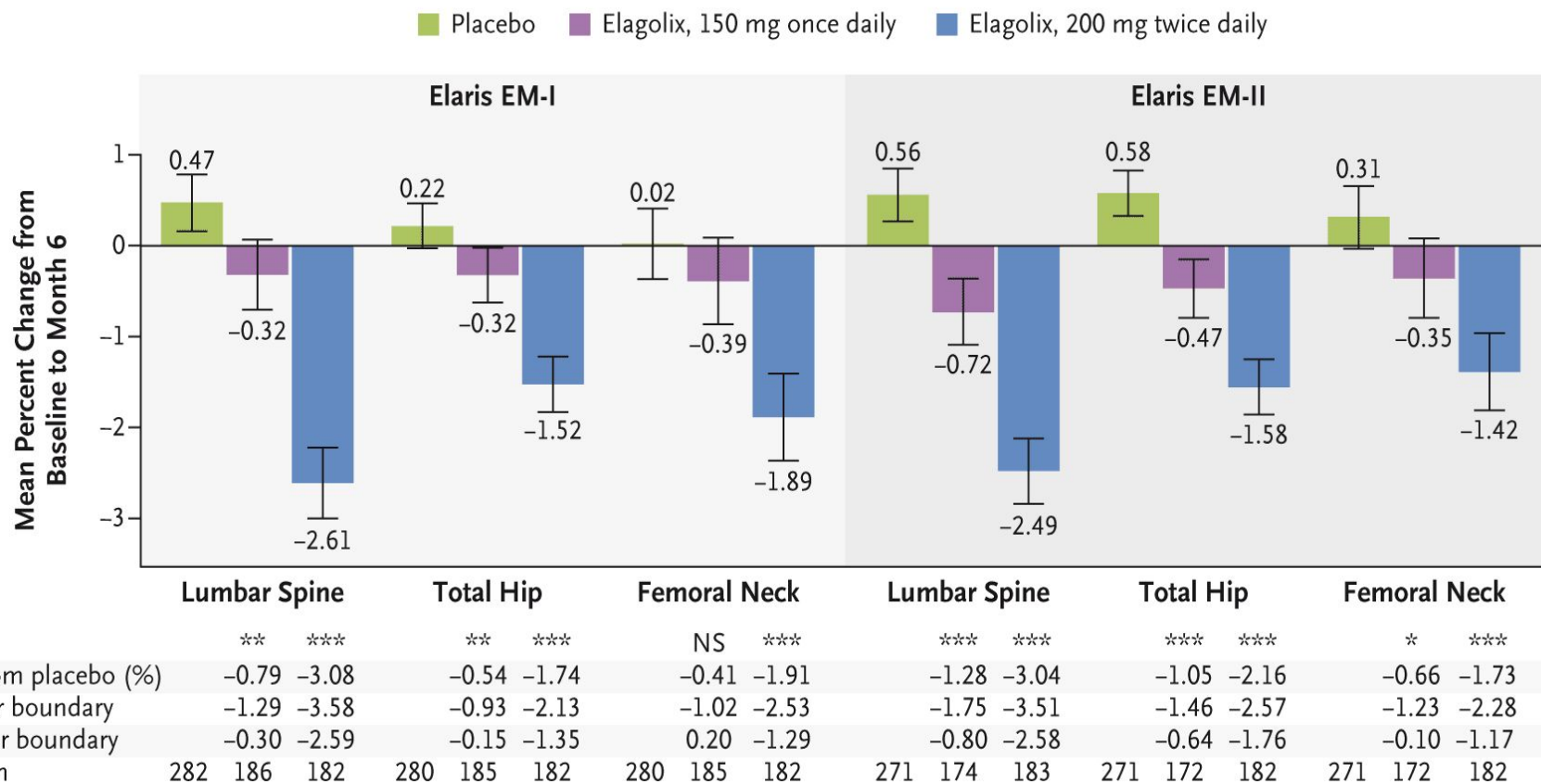
**B Elaris EM-II**



Difference from placebo — % (97.5% CI)	21 (12–30)	50 (41–58)	21 (12–30)	52 (43–60)	13 (4–23)	21 (12–31)	11 (1–21)	22 (12–31)
Risk ratio (97.5% CI)	1.9 (1.4–2.5)	3.2 (2.5–4.0)	1.8 (1.3–2.3)	3.1 (2.4–3.8)	1.4 (1.1–1.6)	1.6 (1.3–1.9)	1.3 (1.0–1.5)	1.5 (1.2–1.8)
Two-sided P value	<0.001	<0.001	<0.001	<0.001	0.003	<0.001	0.01	<0.001

**Figure 1. Reduction in Dysmenorrhea and Nonmenstrual Pelvic Pain.**

Shown are the percentages of women in whom the two primary end points (clinically meaningful reduction in dysmenorrhea or in nonmenstrual pelvic pain, as measured by the decreased or stable use of rescue analgesic agents) were reported at 3 months and 6 months in Elaris EM-I (Panel A) and Elaris EM-II (Panel B). In Elaris EM-I, 3-month data are provided for 373 women who received placebo, 248 who received the lower elagolix dose (150 mg once daily), and 244 who received the higher elagolix dose (200 mg twice daily); the corresponding 6-month data are provided for 372, 247, and 243 women. In Elaris EM-II, 3-month data are provided for 353 women who received placebo, 221 who received the lower elagolix dose, and 225 who received the higher elagolix dose; the corresponding 6-month data are provided for 355, 221, and 225 women. CI denotes confidence interval.



**Figure 2. Mean Percent Change from Baseline to Month 6 in Bone Mineral Density.**

At 6 months, all the percent differences in bone mineral density between the elagolix groups and the placebo group were significant, except for the between-group difference at the femoral neck in Elaris EM-I. One asterisk indicates  $P < 0.05$ , two asterisks  $P < 0.01$ , three asterisks  $P < 0.001$ , and NS not significant. The I bars indicate 95% confidence intervals.



# Выводы

- Как более высокие, так и более низкие дозы элаголикса были эффективны в улучшении дисменореи и неменструальной боли в области таза в течение 6-месячного периода у женщин с болью, связанной с эндометриозом. Две дозы элаголикса были связаны с гипоэстрогенными побочными эффектами.
- 25 июля 2018 года FDA (Управление по контролю качества пищевых продуктов и лекарственных препаратов США) разрешило применять препарат элаголикс *elagolix* (торговое название Орилисса/*Orilissa*) для купирования интенсивной и умеренной тазовой боли при эндометриозе. Это лекарственное средство было разработано учеными из фармацевтической компании *AbbVie*.
- Элаголикс является антагонистом рецептора гонадотропин-высвобождающего гормона.
- Положительное решение FDA было принято после изучения результатов клинических исследований фазы 3, в которых принимали участие около 1 700 женщин.

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Arch Gynecol Obstet. 2017 Apr;295(4):827-832. doi: 10.1007/s00404-017-4328-6. Epub 2017 Mar 3.

## Research development of a new GnRH antagonist (Elagolix) for the treatment of endometriosis: a review of the literature.

Alessandro P<sup>1</sup>, Luigi N<sup>2</sup>, Felice S<sup>2</sup>, Maria PA<sup>3</sup>, Benedetto MG<sup>3</sup>, Stefano A<sup>3</sup>.

### Author information

### Abstract

**PURPOSE:** Limited studies have reported the efficacy of GnRH antagonist on endometriosis symptoms. The aim of our study was to review all available trials to investigate the medical treatment of endometriosis with only GnRH antagonists, with special attention to pharmacodynamic activity, safety, and efficacy.

**METHODS:** Pub Med and Scienccdirect database were searched using terms of "endometriosis treatment", "GnRH antagonist", and "Elagolix". The search was limited to clinical studies published in English. Title and abstract were screened to identify relevant articles.

**RESULTS:** Five studies covering use of GnRH antagonist were found. A phase 1 study evaluated the safety, pharmacokinetics, and inhibitory effects on gonadotropins and estradiol of single dose and 7 day elagolix administration to healthy premenopausal women; two phase II studies evaluated efficacy in patient with endometriosis. Moreover, there are two Phase III clinical trials just completed.

**CONCLUSION:** GnRH antagonists may have the advantage of oral administration and lower incidence of adverse events. Currently, only Phase II studies have been published demonstrating promising results in terms of efficacy, safety, and tolerability. From the results of the phase III studies, elagolix may become a valuable addition to the armamentarium of pharmacological agents to treat endometriosis-related pain.

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**Review** Overview of elagolix for the treatment of endometriosis [Expert Opin Drug Metab Toxicol...]

Suppression of gonadotropins and estradiol in premenopausal w [J Clin Endocrinol Metab. 2009]

Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Ant [N Engl J Med. 2017]

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**Table ES3. Mean Pain Scores in Randomized Controlled Trials of Elagolix**

		Dysmenorrhea			Nonmenstrual Pelvic Pain		
		Baseline	Week 12	Score Change	Baseline	Week 12	Score Change
EM-I <sup>24</sup>	Placebo	2.2	1.9	-0.3	1.6	1.3	-0.3
	Elagolix 150 QD	2.2	1.2	-1.0*	1.6	1.2	-0.4*
	Elagolix 200 BID	2.2	0.4	-1.8*	1.6	0.9	-0.7*
EM-II <sup>24</sup>	Placebo	2.2	1.8	-0.4	1.6	1.2	-0.4
	Elagolix 150 QD	2.2	1.2	-1.0*	1.7	1.1	-0.6*
	Elagolix 200 BID	2.1	0.4	-1.7*	1.6	0.9	-0.7*
Tulip PETAL <sup>22</sup>	Placebo	1.4	0.9	-0.5±	1.0	0.7	-0.3±
	Elagolix 150 QD	1.3	0.5	-0.8±	1.1	0.7	-0.4±
	Leuprorelin acetate	1.3	0.13	-1.2±	0.9	0.4	-0.5±
Lilac PETAL <sup>25</sup>	Placebo	1.2	1.0	-0.2	1.0	0.6	-0.4
	Elagolix 150 QD	1.4	0.6	-0.8*	0.9	0.6	-0.3
PETAL <sup>23</sup>	Elagolix 150 QD	NR	NR	-1.4±	NR	NR	-1.0±
	DMPA-SC	NR	NR	-1.5±	NR	NR	-0.9±

Data were digitized from published charts and should be interpreted with caution; \*p<0.05 for LS mean change versus placebo, ±within-arm statistical testing not performed; QD=daily; BID=twice daily; DMPA-SC=subcutaneous depot medroxyprogesterone; NR=not reported



# Практическая значимость

- Министерством Здравоохранения Республики Казахстан разработан и утвержден клинический протокол «Эндометриоз» (разработчики Дощанова А.М., Тулетова А.С., утвержденного Экспертной комиссией по вопросам Министерства здравоохранения Республики
- В Республике Казахстан с 2014 года март месяц официально признан предложенного Международной ассоциацией эндометриоза, по инициативе и содействию Казахстанской ассоциацией эндометриоза (президент Дощанова А. М., секретарь Тулетова А.С.).

