Preconceptional Care to Optimise Maternal and Neonatal Outcome
Sampoorna
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FEDERATION OF OBSTETRIC AND GYNAECOLOGICAL SOCIETIES OF INDIA

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Har Ghar FOGSIAN

FOGSI Endometriosis Update

Expert Consensus Meeting

Elagolix - Redefining the Endometriosis Therapy Landscape

President's Message

Dear Colleagues,

It gives me immense pleasure and pride to present to you this special edition of *Times of Gynaecology* titled 'Elagolix - Redefining the Endometriosis Therapy Landscape'

Endometriosis is a recognised global health concern, affecting approximately 6–10% of women worldwide. This debilitating condition manifests as dysmenorrhoea, chronic pelvic pain, dyspareunia, dyschezia, fatigue, depression and infertility, profoundly affecting a woman's physical, emotional and social well-being. The associated socioeconomic burden is substantial, with increased hospitalisations, reduced productivity and compromised quality of life.

Traditional medical therapies for endometriosis, though beneficial, are often limited by side effects such as symptom flare and hypo-oestrogenic complications. In this context, Elagolix, a novel oral non-peptide gonadotropin-releasing hormone (GnRH) antagonist, represents a significant advancement.

Through this special issue, we aim to highlight the evolving clinical implications of Elagolix and reinforce our collective efforts in improving outcomes for women living with endometriosis.

I hope this edition serves as a useful resource in guiding informed clinical decisions and empowering us to deliver better outcomes for patients.

Best wishes!

Dr. Sunita Tandulwadkar
MD FICS FICOG

From left to right (sitting): Dr. Sampath Kumari, Dr. P M Gopinath, Dr. Jayam kannan, Dr. Sunita Tandulwadkar, Dr. Madhuri Patel, Dr. J B Sharma, Dr. R M Saraogi

From left to right (standing): Dr. K U Kunjumoideen, Dr. Nilesh Balkawade, Dr. Kailash Ochwani, Dr. Dibyendu Banerjee, Dr. Brajbala Tiwari, Dr. Basab Mukherjee, Dr. Ashwini Kale, Dr. Subash Mallya, Dr. Chaitanya Ganapule, Dr. Mehul Sukhadiya, Dr. Prashanth Adiga, Dr. Abhinibesh Chatterjee

Times of Gynaecology
Elagolix - Redefining the Endometriosis Therapy Landscape

Impact of Endometriosis

Endometriosis, a condition triggered by excessive oestrogen production from the ovaries,[1] is characterised by the growth of endometrial tissue outside the uterus.[2]

Endometriosis is one of the most common gynaecological disorders, affecting around 10% of women of reproductive age globally.[3]

According to the WHO, **196 million** women are affected worldwide[3]

Approximately, **42 million** women are affected in India[3]

The prevalence is estimated to be up to **50%** among women with infertility or those undergoing diagnostic laparoscopy for pelvic pain.[4]

Symptoms of endometriosis can vary widely and may evolve over time.[5] Common symptoms include:

- Dysmenorrhoea[2]
- Non-menstrual pelvic pain[3]
- Dyspareunia[2]
- Chronic pelvic pain[5]
- Dyschezia[5]
- Dysuria[2]
- Metrorrhagia[5]
- Diarrhoea[5]
- Constipation[5]
- Infertility[5]
- Gastrointestinal and urinary symptoms[4]

This disease is associated with significant morbidity, primarily due to pain and infertility. Additionally, endometriosis-associated pain markedly reduces quality of life, affecting physical and mental well-being as well as sexual and social health.[4]

Current treatment trends

According to the FOGSI Good Clinical Practice Recommendations published in March 2024, pharmacological treatment remains the primary approach for managing endometriosis. Given its chronic and progressive nature, patients require a long-term treatment strategy.[6,7] However, the use of the medical therapy is often limited by adverse effects.[6]

Medical therapies for the management of endometriosis and their challenges are listed below:[7-16]

NSAIDs

Special remark:

- Effectively relieve dysmenorrhoea[6]

Challenge:

- No effect on long-term disease progression[6,7]

COCs

Special remark:

- Oral[7]

Challenges:

- Continuous use preferred[7]
- Risk of disease progression[7]
- Breakthrough bleeding, decreased libido, depressed mood, headache, weight gain and thromboembolism[8-10]

Progestins

Special remark:

- Oral, LNG-IUS - ease of use; beneficial in dysmenorrhoea[7]

Challenges:

- Headache, bloating, weight gain, breakthrough bleeding, hirsutism and acne[7,10]
- Progestin resistance[11]

Dienogest

Special remark:

- Formulated for endometriosis[7]
- Can be used for up to 52 weeks[7]

Challenges:

- Decreases lumbar spine bone density[7]
- Abnormal uterine bleeding, headache, bleeding irregularities, vaginal dryness and mood disorders[7,12]
- Progestin resistance[13]
- Possible association with breast cancer[14]

GnRH agonists

Special remark:

- Short term use[7]
- Add-back therapy recommended[7]

Challenges:

- Injectable[7]
- Flare effect[15]
- Bone loss and other hypoestrogenic symptoms[7]
- Uncertain effectiveness[7]

Aromatase inhibitors

Special remark:

- Add-back therapy recommended[7]
- Useful for drug-resistant rectovaginal endometriosis[7]

Challenges:

- Arthralgia, myalgia and decreased bone mineral density (BMD)[7]

Anti-angiogenic drugs

Special remark:

- Non-hormonal treatment[7]
- Do not prevent ovulation[1]

Challenges:

- Nausea, headache, dizziness, fatigue and constipation[16]

There remains an unmet need for an effective long-term oral treatment capable of managing symptoms of endometriosis, while alleviating the impact of side effects.[17]

Elagolix is the first oral GnRH antagonist indicated for moderate-to-severe endometriosis-associated pain, approved by the United States Food and Drug Administration (US FDA).[18]

Elagolix was approved following successful trials conducted over a decade.[18-22]

Country	Year of approval
United States of America	July 2018
Canada	October 2018
Puerto Rico	July 2018
Bangladesh	November 2020
Israel	December 2022
India	August 2024
Pakistan	October 2024

Elagolix represents a paradigm shift from injectable GnRH agonists by delivering rapid, dose-dependent suppression of ovarian oestradiol without the initial clinical "flare", a shorter half-life and quick reversibility of ovarian function on discontinuation.[23]

The guidelines from ESHRE, CNGOF and AAFP collectively support the use of Elagolix as an effective treatment for the management of endometriosis-related pain.[24-26]

Properties of Elagolix at a glance:

Formulation and dosing: Oral tablets with 150 mg OD (for low-to-moderate pain) or 200 mg BID (for moderate-to-severe pain or dyspareunia)[18]

Pharmacology: Short plasma half-life (~4-6 hours) with competitive, reversible GnRH receptor blockade enabling precise, dose-tunable hormone control[18,27,28]

Oestradiol suppression: Dose-dependent[27]

150 mg OD → Partial suppression (median ≈ 42 pg/mL)[18]

200 mg BID → Near-complete suppression (≈ 12 pg/mL)[18]

Clinical benefits: Oral convenience, no flare effect and rapid onset/offset[23,27]

Regulatory note: First oral, FDA-approved treatment for endometriosis-associated pain in >10 years[18]

ESHRE: European Society of Human Reproduction and Embryology; CNGOF: Collège National des Gynécologues et Obstétriciens Français; AAFP: American Academy of Family Physicians

Understanding the potential of Elagolix

Advantages of oral GnRH agonists vs. GnRH antagonists

GnRH antagonists competitively bind to the GnRH receptors in the pituitary gland. By blocking endogenous GnRH signalling, they suppress luteinising hormone (LH) and follicle-stimulating hormone (FSH), leading to dose-dependent reduced production of oestradiol and progesterone.[18]

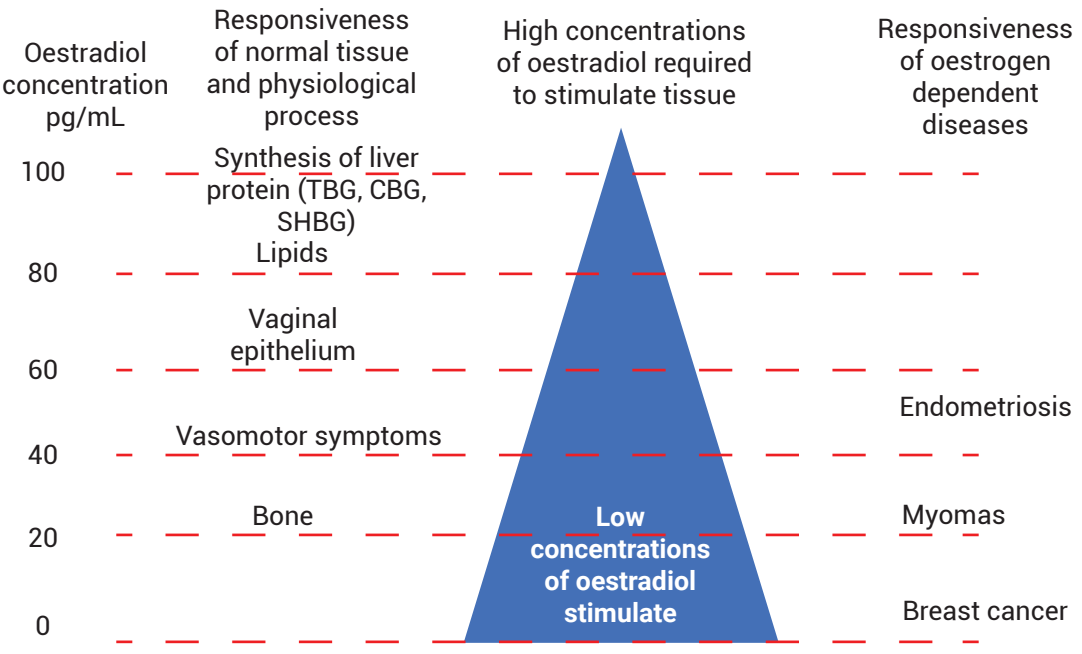
Unlike GnRH agonists, which induce a hypo-oestrogenic state through complete suppression of the hypothalamic–pituitary–ovarian (HPO) axis, GnRH antagonists work through dose-dependent suppression of oestradiol. This mechanism reduces the risk of hypoestrogenic side effects such as hot flushes, vaginal dryness and reduced BMD, while maintaining therapeutic efficacy.[27,29]

Another important distinction is that GnRH antagonists do not trigger the initial stimulation or "flare" effect seen with GnRH agonists, during which symptoms may temporarily worsen in the first 1–2 weeks of therapy.[29]

Targeting therapeutic oestradiol window in endometriosis

The oestrogen threshold hypothesis suggests **that oestradiol levels influence both disease activity and bone health, with different tissues showing variable sensitivity to circulating oestradiol concentrations. Oestradiol concentrations above 60 pg/mL are often associated with the growth of endometriotic lesions, whereas concentrations in the range of 10–20 pg/mL can induce regression of lesions but are also linked to bone loss, vasomotor symptoms and other concerns** (Figure 1).[30,31]

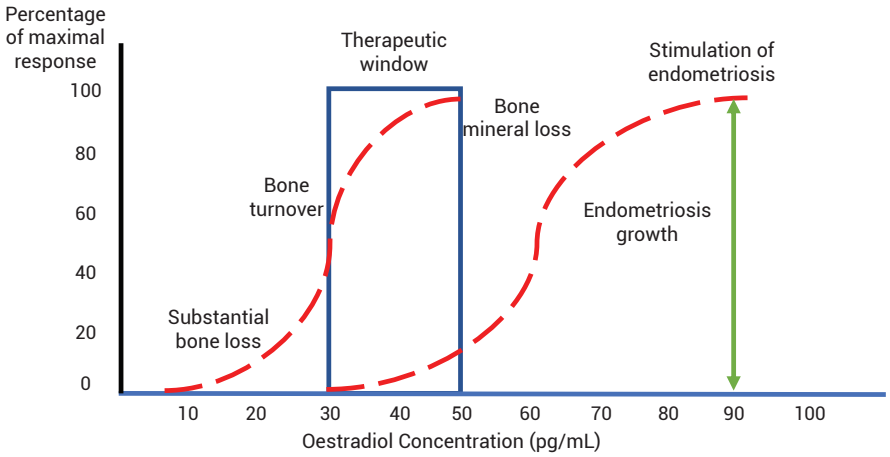
Figure 1: Oestrogen levels and effects on organs



TBG: Thyroxine-binding globulin; CBG: Corticosteroid-binding globulin; SHBG: Sex hormone-binding globulin. (Adapted from: Barbieri RL. *Am J Obstet Gynecol.* 1992;166(2):740-5.)[31]

Evidence indicates the existence of an "oestradiol therapeutic window", in which oestradiol levels between 30–45 pg/mL may suppress endometriotic lesion growth while minimising adverse skeletal effects. For example, regression of endometriotic lesions can be consistently achieved at around 30 pg/mL, whereas higher levels (100–300 pg/mL) promote lesion growth without affecting BMD. Conversely, very low oestradiol concentrations (10–20 pg/mL) cause lesion regression but significant bone loss (Figure 2).[30]

Figure 2: The oestrogen threshold theory

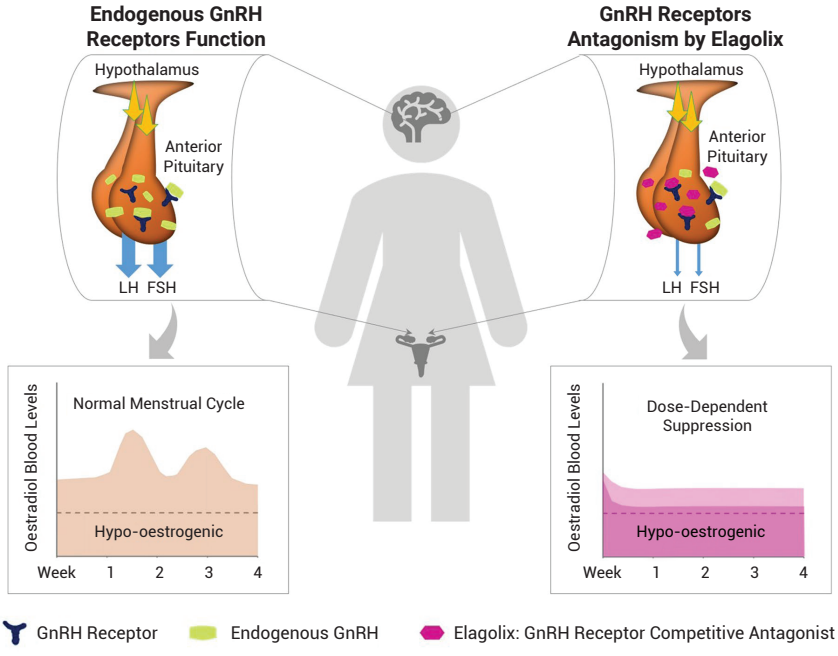


(Adapted from: Barbieri RL. *Am J Obstet Gynecol.* 1992;166(2):740-5.)[30,31]

Supporting this concept, studies have shown that women with oestradiol levels >10 pg/mL had significantly higher BMD at the lumbar spine (+14%), proximal femur (+6%) and total skeleton (+7%). Similarly, women with endogenous oestradiol levels <5 pg/mL had a 50–70% higher risk of hip and spine fractures compared with those in the 5–9 pg/mL range.[31]

Elagolix reduces oestradiol in a dose-dependent manner, about 42 pg/mL with 150 mg OD provides partial oestrogen suppression, thus offering a bone-safe alternative, whereas Elagolix 200 mg BID provides near-complete suppression of oestrogen (~12 pg/mL) with stronger symptomatic control (Figure 3).[18,27,28] Thus, Elagolix, as a GnRH antagonist, offers the potential for dose adjustment to balance efficacy and safety.[32-34] **Elagolix 150 mg maintains serum oestrogen levels within the oestrogen threshold window and hence, does not require add-back therapy support.**

Figure 3: Mechanism of action of GnRH receptor antagonism in the anterior pituitary prevents LH/FSH release, leading to rapid, dose-dependent suppression of ovarian oestradiol (E2) without the initial flare of GnRH agonists



GnRH: gonadotropin-releasing hormone; LH: Luteinising hormone; FSH: Follicle-stimulating hormone. (Adapted from: Shebley M *et al. Clin Pharmacokinet.* 2020;59(3):297-309.)[27]

Clinical efficacy of Elagolix

Evidence from landmark trials

The clinical efficacy of Elagolix was established in two pivotal 6-month, Phase III, multicentre, double-blind, randomised, placebo-controlled trials, namely Elaris EM-I (n=872) and EM-II (n=817), in women with surgically diagnosed moderate-to-severe endometriosis-associated pain. The Elaris EM-I trial was conducted in USA and Canada. **The Elaris EM-II trial covered wider geographies: Argentina, Austria, Australia, Brazil, Czech Republic, Hungary, Italy, New Zealand, Poland, South Africa, Spain, the USA and the United Kingdom.**[34,35]

Later, two open-label extensions of EM-I and EM-II were conducted, named EM-III and EM-IV, respectively. Women who had received Elagolix in the pivotal trials and agreed to continue were treated with the same dose (150 mg OD or 200 mg BID) for an additional **6 months, yielding a total of 12 months of continuous therapy, followed by an additional 12-month observational period.**[32]

Co-primary endpoints for these trials were the proportions of women with a clinically meaningful reduction **(with no increase in rescue analgesics)** in dysmenorrhoea and non-menstrual pelvic pain (NMPP). Key secondary endpoints included change in pain scores and dyspareunia response.[32,34]

The pivotal Elaris trials (EM-I to EM-II) consistently demonstrated the efficacy of Elagolix in reducing endometriosis-associated pain (Table 1).[27]

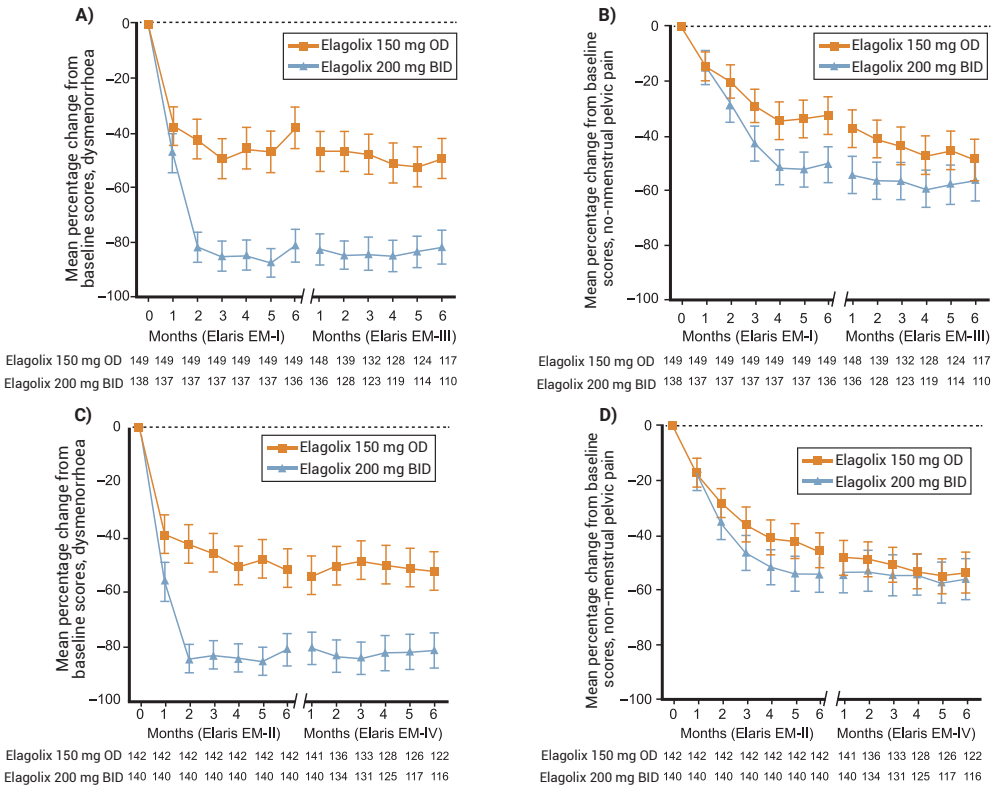
Table 1: Efficacy of Elagolix in EM trials[34]

Endpoint	Timepoint	Elagolix 150 mg OD (%)	Elagolix 200 mg BID (%)
EM-I			
Dysmenorrhoea	3 months	46.4	75.8
Dysmenorrhoea	6 months	42.1	75.3
NMPP	3 months	50.4	54.5
NMPP	6 months	45.7	62.1
EM-II			
Dysmenorrhoea	3 months	43.4	72.4
Dysmenorrhoea	6 months	46.2	76.9
NMPP	3 months	49.8	57.8
NMPP	6 months	51.6	62.2

Note: $p < 0.001$ for both endpoints in EM-I and EM-II. NMPP: Non-menstrual pelvic pain.

The long-term extension studies (EM-III and EM-IV) confirmed sustained benefits over 12 months, reinforcing the long-term efficacy of Elagolix in managing endometriosis-associated pain (Table 2, Figure 4).[32]

Figure 4: Mean percent change from baseline in dysmenorrhoea (A and D), non-menstrual pelvic pain (B and E)



OD: Once daily; BID: Twice daily; EM: Endometriosis. (Adapted from: Surrey E *et al. Obstet Gynecol.* 2018;132(1):147-60.)[32]

Table 2: Elagolix long-term efficacy (EM-III and EM-IV)[32]

Endpoint	Duration	EM-III 150 mg OD (%)	EM-III 200 mg BID (%)	EM-IV 150 mg OD (%)	EM-IV 200 mg BID (%)
Dysmenorrhoea	6 months	40.3%	80.1%	50.7%	76.4%
	12 months	52.1%	78.2%	50.8%	75.9%
Non-menstrual pelvic pain	6 months	49.7%	70.6%	57.7%	63.6%
	12 months	67.5%	69.1%	66.4%	67.2%
Dyspareunia	6 months	37.2%	58.7%	43.5%	62.0%
	12 months	45.2%	60.0%	45.9%	58.1%

Elagolix provided additional benefits beyond primary pain endpoints:[32]

- ↑ Dose-dependent improvement in dyspareunia
- ↑ More women with meaningful improvement (PGIC scale)
- ↑ Enhanced quality of life (EHP-30 scores at 3 and 6 months)
- ↓ Lower opioid consumption
- ↓ Reduced rescue analgesic use

These findings highlight the role of Elagolix in delivering sustained symptom relief and reducing medication burden in women with endometriosis (Table 3).[32,34]

Table 3: Key secondary efficacy endpoints

Endpoint	150 mg OD	200 mg BID
Dyspareunia response at 6 months[32]	37.2% (EM-III)	58.7% (EM-III)
	43.5% (EM-IV)	62.0% (EM-IV)
Rescue analgesic use at 3 and 6 months[34]	Reduced vs. placebo	Greater reduction vs. placebo
PGIC ("much/very much improved") at 6 months[34]	Much improved vs. placebo	Very much improved vs. placebo
EHP-30 quality of life at 3 and 6 months[34]	Significant improvement	Significant improvement
Opioid use at 12 months[32]	Reduced	Greater reduction seen

PGIC: Patient Global Impression of Change; EHP: Endometriosis Health Profile.

Evidence from extended analysis and meta-analysis

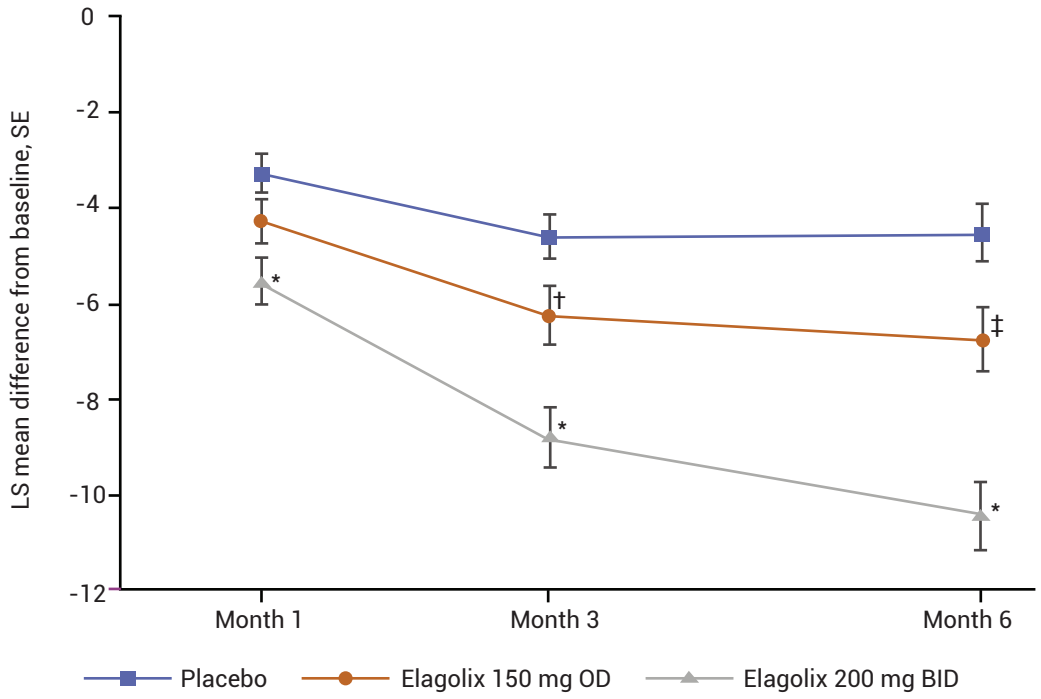
An extended analysis of the Phase III Elaris EM-I trial evaluated the effect of Elagolix on fatigue. Fatigue was assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 6a questionnaire T-score at months 1, 3 and 6.[28]

Elagolix demonstrated a significant reduction in fatigue with both doses compared with placebo at 6 months (Figure 5).

150 mg OD: Fatigue T-score ↓ −2.21

200 mg BID: Fatigue T-score ↓ −5.90

Figure 5: Reduction in PROMIS Fatigue Questionnaire T-scores



p-value vs. placebo: *< 001; †<.01, ‡<.05. BID: Twice daily; OD: Once daily; SE: Standard error (Adapted from: Surrey ES *et al. Fertil Steril.* 2019;112(2):298-304.e3.).[28]

Additionally, a recent **ACOG-published systematic review and meta-analysis (August 2025)** established Elagolix as one of the most effective pharmacologic interventions for endometriosis-associated pain (Figure 6).[29]

Figure 6: Head-to-head comparison of all intervention groups analysed by the Dysmenorrhoea Network

Elagolix												
-0.41(-6.24, 5.42)	Gestrinone											
-1.16(-5.27, 2.95)	-0.76(-4.89, 3.38)	Leuprolide										
-1.07(-6.25, 4.11)	-0.66(-6.38, 5.05)	0.09(-3.85, 4.04)	Leuprolide +COCP									
-1.44(-7.25, 4.36)	-1.04(-6.87, 4.79)	-0.28(-4.39, 3.83)	-0.38(-6.07, 5.32)	Relugolix								
-1.80(-5.56, 1.96)	-1.39(-7.45, 4.67)	-0.64(-5.07, 3.80)	-0.73(-6.17, 4.71)	-0.35(-6.39, 5.68)	Relugolix +COCP							
-1.76(-6.36, 2.84)	-1.36(-7.06, 4.35)	-0.60(-4.53, 3.33)	-0.69(-6.00, 4.62)	-0.32(-6.00, 5.37)	0.04(-4.85, 4.93)	ASP1707						
-2.08(-7.90, 3.75)	-1.67(-8.41, 5.07)	-0.91(-6.24, 4.41)	-1.01(-6.72, 4.71)	-0.63(-7.36, 6.09)	-0.28(-6.33, 5.78)	-0.31(-6.49, 5.86)	Goserelin					
-2.07(-6.19, 2.04)	-1.67(-7.00, 3.66)	-0.91(-4.27, 2.45)	-1.01(-4.95, 2.94)	-0.63(-5.94, 4.68)	-0.28(-4.71, 4.16)	-0.31(-4.91, 4.28)	0.00(-4.13, 4.14)	COCP				
-2.32(-6.11, 1.46)	-1.92(-7.99, 4.16)	-1.16(-5.61, 3.29)	-1.25(-6.71, 4.20)	-0.88(-6.93, 5.17)	-0.52(-4.65, 3.60)	-0.56(-5.47, 4.35)	-0.25(-6.32, 5.82)	-0.25(-4.70, 4.20)	Vitamin D			
-2.22(-8.02, 3.59)	-1.81(-8.54, 4.91)	-1.06(-6.36, 4.25)	-1.15(-6.84, 4.54)	-0.77(-7.48, 5.93)	-0.42(-6.46, 5.62)	-0.46(-6.61, 5.70)	-0.14(-5.97, 5.68)	-0.14(-4.25, 3.96)	0.11(-5.95, 6.16)	Letrozole+ COCP		
-2.27(-8.09, 3.54)	-1.87(-8.60, 4.87)	-1.11(-6.43, 4.20)	-1.21(-6.91, 4.50)	-0.83(-7.54, 5.89)	-0.48(-6.52, 5.57)	-0.51(-6.68, 5.66)	-0.20(-6.03, 5.64)	-0.20(-4.32, 3.92)	0.05(-6.01, 6.11)	-0.06(-5.87, 5.76)	Etono--gestrel	
-2.43(-7.21, 2.34)	-2.03(-8.76, 4.71)	-1.27(-6.59, 4.05)	-1.37(-7.55, 4.82)	-0.99(-7.71, 5.73)	-0.64(-5.69, 4.42)	-0.67(-6.38, 5.03)	-0.36(-7.09, 6.38)	-0.36(-5.68, 4.96)	-0.11(-5.18, 4.96)	-0.22(-6.93, 6.50)	-0.16(-6.89, 6.56)	Vitamin C+ Vitamin E
-2.45(-7.20, 2.31)	-2.04(-8.76, 4.68)	-1.28(-6.58, 4.02)	-1.38(-7.54, 4.79)	-1.00(-7.70, 5.70)	-0.65(-5.68, 4.38)	-0.68(-6.37, 5.00)	-0.37(-7.09, 6.35)	-0.37(-5.67, 4.93)	-0.12(-5.17, 4.93)	-0.23(-6.93, 6.47)	-0.17(-6.88, 6.54)	-0.01(-5.84, 5.82)
-2.91(-7.66, 1.84)	-2.50(-9.22, 4.22)	-1.75(-7.05, 3.55)	-1.84(-8.01, 4.32)	-1.47(-8.17, 5.23)	-1.11(-6.14, 3.92)	-1.15(-6.83, 4.54)	-0.83(-7.55, 5.88)	-0.84(-6.14, 4.46)	-0.59(-5.63, 4.46)	-0.69(-7.39, 6.01)	-0.64(-7.34, 6.07)	-0.48(-6.30, 5.35)
-2.89(-5.28, -0.50)	-2.48(-7.80, 2.84)	-1.72(-5.07, 1.62)	-1.82(-6.41, 2.78)	-1.44(-6.74, 3.85)	-1.09(-3.99, 1.82)	-1.13(-5.06, 2.81)	-0.81(-6.13, 4.50)	-0.81(-4.16, 2.53)	-0.56(-3.50, 2.37)	-0.67(-5.96, 4.62)	-0.61(-5.92, 4.69)	-0.45(-4.59, 3.68)
-3.15(-7.90, 1.61)	-2.74(-9.46, 3.98)	-1.99(-7.29, 3.31)	-2.08(-8.24, 4.09)	-1.70(-8.41, 5.00)	-1.35(-6.38, 3.68)	-1.39(-7.07, 4.30)	-1.07(-7.79, 5.65)	-1.07(-6.37, 4.23)	-0.82(-5.87, 4.22)	-0.93(-7.63, 5.77)	-0.87(-7.58, 5.84)	-0.71(-6.54, 5.12)

Linzagolix												
-0.46(-6.27, 5.35)	Elagolix + ABT											
-0.44(-4.55, 3.67)	0.02(-4.08, 4.13)	Placebo										
-0.70(-4.81, 3.41)	-0.24(-6.05, 5.57)	-0.26(-4.37, 3.85)	Linzagolix + ABT									

In the management of dysmenorrhoea, Elagolix demonstrated better pain reduction as compared to all other interventions (including injectable GnRH antagonists, agonists, progestins, COC pills etc.).

COCP: Combined oral contraceptive pills; ABT: Add-back therapy. (Adapted from: Kou L *et al. Obstet Gynecol.* 2025;146(2):e23-e35.)[36]

Figure 7: Head-to-head comparison of all intervention groups analysed by the Dyspareunia Network

Vitamin C+ Vitamin E												
-0.39(-4.09, 3.31)	Gestrinone											
-0.45(-4.14, 3.24)	-0.06(-3.77, 3.65)	Letrozole+ COCP										
-0.56(-3.98, 2.85)	-0.17(-3.44, 3.09)	-0.11(-3.34, 3.11)	Leuprolide +COCP									
-0.56(-4.29, 3.17)	-0.17(-3.91, 3.58)	-0.11(-3.47, 3.26)	0.01(-3.26, 3.27)	Goserelin								
-0.75(-3.48, 1.97)	-0.36(-3.24, 2.52)	-0.30(-3.27, 2.67)	-0.19(-2.75, 2.37)	-0.20(-3.21, 2.82)	Elagolix							
-0.79(-3.63, 2.06)	-0.40(-3.27, 2.48)	-0.34(-2.69, 2.02)	-0.22(-2.43, 1.99)	-0.23(-2.63, 2.18)	-0.03(-1.85, 1.78)	COCP						
-0.90(-3.71, 1.90)	-0.51(-2.92, 1.90)	-0.45(-3.28, 2.37)	-0.34(-2.55, 1.87)	-0.34(-3.21, 2.52)	-0.15(-1.73, 1.43)	-0.12(-1.68, 1.45)	Leuprolide					
-0.79(-4.54, 2.96)	-0.40(-4.16, 3.37)	-0.34(-3.73, 3.05)	-0.22(-3.51, 3.07)	-0.23(-3.65, 3.20)	-0.03(-3.07, 3.01)	-0.00(-2.44, 2.44)	0.12(-2.78, 3.01)	Triptorelin				
-0.91(-4.60, 2.79)	-0.51(-4.23, 3.20)	-0.46(-4.12, 3.21)	-0.34(-3.74, 3.06)	-0.35(-4.04, 3.35)	-0.15(-3.12, 2.82)	-0.12(-2.93, 2.69)	-0.00(-2.83, 2.82)	-0.12(-3.84, 3.60)	Buserelin			
-1.15(-3.99, 1.70)	-0.76(-3.62, 2.11)	-0.70(-3.50, 2.10)	-0.58(-3.04, 1.87)	-0.59(-3.43, 2.26)	-0.39(-2.20, 1.41)	-0.36(-1.88, 1.16)	-0.24(-1.80, 1.31)	-0.36(-3.23, 2.51)	-0.24(-2.60, 2.12)	Dienogest		
-1.38(-4.63, 1.87)	-0.99(-4.22, 2.24)	-0.93(-4.33, 2.46)	-0.82(-3.81, 2.18)	-0.82(-4.25, 2.61)	-0.63(-3.01, 1.76)	-0.59(-3.04, 1.85)	-0.48(-2.64, 1.68)	-0.59(-4.05, 2.86)	-0.48(-3.87, 2.92)	-0.23(-2.68, 2.21)	ASP1707	
-1.82(-5.21, 1.56)	-1.43(-5.08, 2.21)	-1.37(-5.02, 2.27)	-1.26(-4.62, 2.10)	-1.26(-4.94, 2.41)	-1.07(-3.73, 1.59)	-1.04(-3.82, 1.74)	-0.92(-3.66, 1.82)	-1.04(-4.74, 2.66)	-0.92(-4.56, 2.73)	-0.68(-3.45, 2.10)	-0.44(-3.64, 2.75)	Elagolix+ ABT
-1.86(-5.14, 1.43)	-1.47(-5.02, 2.08)	-1.41(-4.96, 2.14)	-1.29(-4.55, 1.96)	-1.30(-4.88, 2.28)	-1.10(-3.63, 1.43)	-1.07(-3.73, 1.58)	-0.96(-3.57, 1.66)	-1.07(-4.68, 2.54)	-0.95(-4.50, 2.60)	-0.71(-3.36, 1.94)	-0.48(-3.56, 2.61)	-0.04(-3.26, 3.19)
-1.80(-4.75, 1.15)	-1.41(-4.66, 1.84)	-1.35(-4.59, 1.89)	-1.23(-4.15, 1.68)	-1.24(-4.52, 2.04)	-1.04(-3.12, 1.03)	-1.01(-3.24, 1.22)	-0.90(-3.07, 1.28)	-1.01(-4.32, 2.29)	-0.89(-4.14, 2.35)	-0.65(-2.88, 1.58)	-0.42(-3.15, 2.31)	0.02(-2.86, 2.91)
-1.86(-4.81, 1.08)	-1.47(-4.72, 1.77)	-1.41(-4.65, 1.83)	-1.30(-4.21, 1.62)	-1.31(-4.58, 1.97)	-1.11(-3.18, 0.97)	-1.08(-3.31, 1.15)	-0.96(-3.13, 1.21)	-1.08(-4.38, 2.23)	-0.96(-4.20, 2.28)	-0.72(-2.94, 1.51)	-0.48(-3.21, 2.24)	-0.04(-2.93, 2.84)
-1.99(-5.42, 1.43)	-1.60(-5.29, 2.08)	-1.54(-5.22, 2.14)	-1.43(-4.83, 1.97)	-1.43(-5.15, 2.28)	-1.24(-3.95, 1.47)	-1.21(-4.04, 1.62)	-1.09(-3.88, 1.70)	-1.21(-4.94, 2.53)	-1.09(-4.77, 2.60)	-0.85(-3.67, 1.98)	-0.61(-3.85, 2.63)	-0.17(-3.54, 3.20)
-2.07(-4.50, 0.36)	-1.68(-4.46, 1.10)	-1.62(-4.40, 1.16)	-1.51(-3.90, 0.89)	-1.51(-4.34, 1.31)	-1.32(-2.55, -0.08)	-1.28(-2.76, 0.19)	-1.17(-2.56, 0.23)	-1.28(-4.14, 1.57)	-1.17(-3.95, 1.62)	-0.92(-2.40, 0.55)	-0.69(-2.85, 1.47)	-0.25(-2.60, 2.11)

Linzagolix +ABT												
0.06(-2.15, 2.27)	Linzagolix											
-0.07(-2.43, 2.29)	Elagolix+ COCP											
-0.01(-2.77, 2.76)	-0.13(-3.06, 2.80)	Vitamin D										
-0.13(-3.40, 3.14)	-0.19(-3.13, 2.74)	-0.27(-1.94, 1.40)	-0.21(-1.87, 1.46)	-0.08(-2.49, 2.33)	Placebo							
-0.21(-2.42, 1.99)												

In the management of dyspareunia, Elagolix monotherapy was more effective than combination antagonist + add-back, as OCP or add-back interferes with the functions of the HPO axis, leading to unstable efficacy.

COCP: Combined oral contraceptive pills; ABT: Add-back therapy. (Adapted from: Kou L *et al. Obstet Gynecol.* 2025;146(2):e23-e35.)[36]

Clinical safety and tolerability of Elagolix

Common adverse events[32,34]

In the Elaris EM-I to EM-IV trials involving women with moderate or severe endometriosis-associated pain, Elagolix was well tolerated overall.

Adverse events (AEs) were reported in >70% of women across all trial groups, including Elagolix 150 mg, 200 mg and placebo arms.

Severity

- Mostly mild to moderate
- 200 mg BID had higher incidence of hot flush vs. 150 mg and placebo

Common AEs

- Hot flush
- Headache
- Nausea

Effect on bone mineral density[32]

One needs to be cautious about the BMD concerns with the higher dose of Elagolix.

Both Elagolix regimens cause dose-dependent BMD declines.

At 12 months (mean % change in lumbar spine BMD)

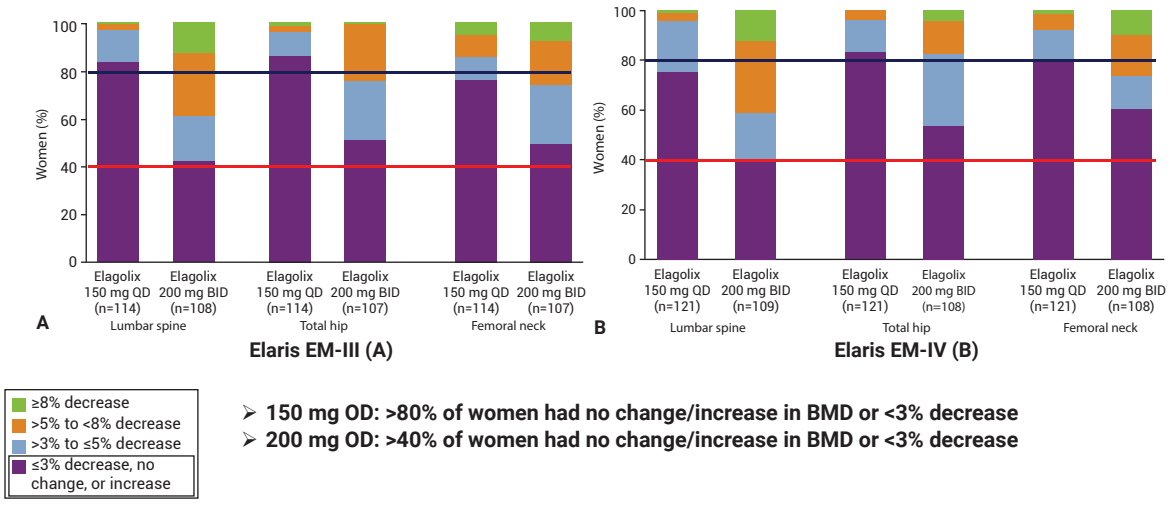
150 mg OD: –0.63%	200 mg BID: –3.91%

<1% change in BMD as compared to baseline is considered to be negligible.

Caution is warranted regarding BMD loss with the higher dose of Elagolix, as the concern increases with prolonged use; accordingly, this dose is approved for continuous treatment for up to 6 months without add-back therapy.

Most importantly, in the EM-III and EM-IV extension studies, 83.3% of women on 150 mg and 42.6% on 200 mg maintained lumbar spine BMD within a 3% change from baseline, with similar results for the total hip and femoral neck (Figure 7).[32]

Figure 7: Mean % change from baseline in BMD after 12 months of Elagolix treatment



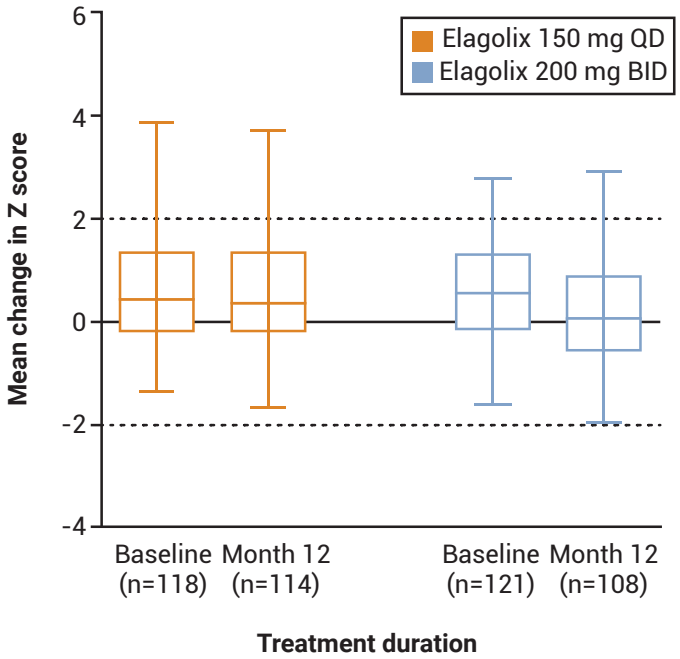
- ≥8% decrease
- >5% to <8% decrease
- >3% to ≤5% decrease
- ≤3% decrease, no change, or increase

- **150 mg OD: >80% of women had no change/increase in BMD or <3% decrease**
- **200 mg OD: >40% of women had no change/increase in BMD or <3% decrease**

BMD: Bone mineral density; EM: Endometriosis; OD: Once daily; BID: Twice daily.
(Adapted from: Surrey E *et al. Obstet Gynecol.* 2018;132(1):147-60.)[32]

No women in the studies had a Z-score below -2.0 (the lower bound of the normal range), indicating no cases of clinically significant osteoporosis during the study (one case had a BMD Z score of -2) (Figure 8).[32]

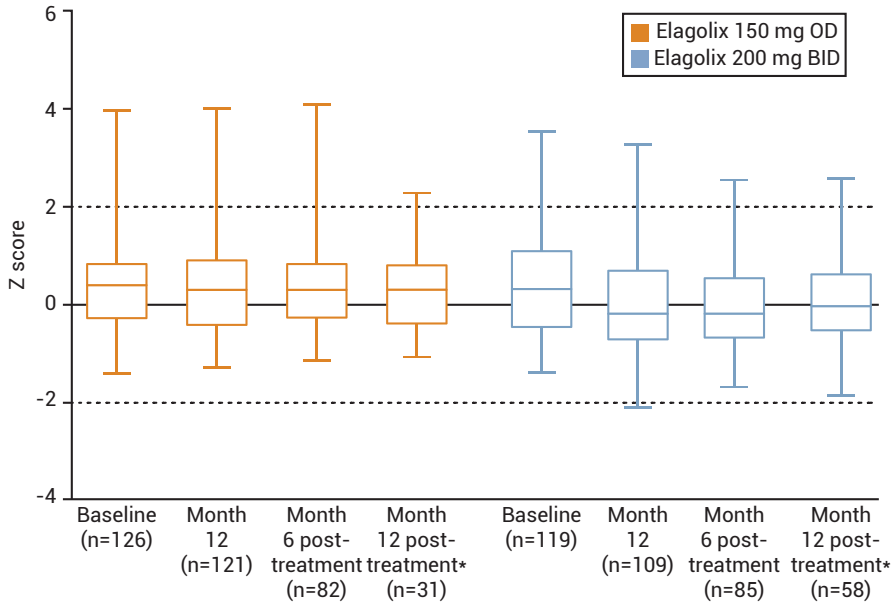
Figure 8: Z-score ≤ –2.0 after 12 months of treatment (none in EM-III; one case in EM-IV with 200 mg BID)



(Adapted from: Surrey E *et al. Obstet Gynecol.* 2018;132(1):147-60.)[32]

Additionally, after cessation of treatment in Elaris EM-IV, BMD values returned towards baseline values during the post-treatment follow-up period (Figure 9).[32]

Figure 9: Trend showing improvement in BMD Z-scores, suggesting partial recovery of BMD following cessation of treatment



*Elaris EM-III was not designed to evaluate post-treatment bone mineral density recovery for all women.
(Adapted from: Surrey E *et al. Obstet Gynecol.* 2018;132(1):147-60.)[17]

Comparative safety analysis

Comparison with oral contraceptives

In EM-I and EM-II, the most frequent adverse events with Elagolix were hot flushes, headache and nausea (≥10%).[32]

On the other hand, oral contraceptives more commonly caused spotting, irregular bleeding, menorrhagia and nausea, along with the added risk of thromboembolism.[3,8] Oral contraceptives are also associated with important contraindications, such as age >35 years, smoking and history of thrombosis, which limit their use in some patients.[7]

Comparison with Dienogest

Elagolix was mainly associated with hot flushes (25–55%) and nausea (12–24.6%), with headaches reported in 19–29.3% of patients.[32] In comparison, Dienogest was linked to breakthrough bleeding in 95%, hot flushes in 50%, headaches in 25% and an overall 100% incidence of AEs among the patients.[37]

Elagolix was also associated with modest, dose-dependent decreases in lumbar spine BMD over 6 months, ranging from –0.3% to –0.7% with the 150 mg OD regimen and –2.5% to –2.6% with the 200 mg BID regimen.[32] In contrast, Dienogest was associated with a BMD reduction of 1.6% ± 2.4% at 24 weeks.[37]

The Indian experience of Elagolix: The first-in-the-world active controlled Phase-III study for Endometriosis management

The first-in-the-world active-controlled Phase-III trial conducted in India compared Elagolix 150 mg with Dienogest 2 mg in premenopausal women with endometriosis-associated pain. This randomised, multicentric, double-blind, non-inferiority study enrolled 230 patients (115 per arm) and evaluated treatment over 24 weeks.[38]

At day 85: Reduction in numeric rating scale pain score with Elagolix (−2.43 ± 1.28) was non-inferior to Dienogest (−2.47 ± 1.26)

At day 169: Reductions remained similar (Elagolix: −4.33 ± 1.46; Dienogest: −4.37 ± 1.28)

Dysmenorrhoea and non-menstrual pelvic pain scores improved comparably in both groups.[38]

- Rescue medication use at Day 169 was almost identical (Elagolix: 17.7% vs. Dienogest: 17.0%
- Responder rates on PGI-C scale were similar (Elagolix: 92.9% vs. Dienogest: 94.6%)
- **Safety:** Both arms had a similar incidence of treatment emergent AEs, with no serious AEs reported

This landmark study demonstrated that Elagolix 150 mg was non-inferior to Dienogest 2 mg for pain reduction in endometriosis and was well tolerated, reinforcing Elagolix as a valuable therapeutic option.[38]

Progestin resistance

The progesterone receptor (PGR) is activated by oestrogen through its receptor, ERα. PGR exists in two forms, PR-A and PR-B, whose levels rise during the proliferative phase of the menstrual cycle and decline after ovulation. Once expressed, PGR suppresses ERα, creating a feedback mechanism. In endometriosis, due to a low ERα:ERβ ratio and elevated oestrogen levels, progesterone resistance develops.[39] Retrospective studies on endometriosis indicate that progesterone resistance may play a role in disease progression and that the status of progesterone receptors is closely linked to response to progestin-based treatments.[40] A study reported that about 33% of patients with endometriosis receiving progestins do not respond to treatment.[41]

The expression of steroidogenic genes in the ovary is controlled by the nuclear receptor subfamily 5, group A, member 1 (NR5A1), also known as steroidogenic factor 1 (SF1). In normal endometrial tissue, SF1 expression is silenced due to extensive promoter methylation. However, in endometriosis, aberrant demethylation of the SF1 promoter leads to increased SF1 expression. This reactivation of SF1 is believed to drive the expression of key steroidogenic enzymes such as STAR, CYP11A1, CYP17A1, and CYP19A1 resulting in the local production of E2 that may promote lesion growth independently of ovarian E2. Notably, SF1 expression in ovarian endometriotic tissue is more than 12,000 times higher than in normal endometrium. The biologically active form of estrogen, E2, aggravates inflammation and tissue growth, as well as the symptoms, including pain, linked to endometriosis.[42,43]

GnRH antagonist reduces aromatase mRNA expression in a dose-dependent manner by inhibiting SF-1 and related transcription factors, leading to decreased E2 production[44]

Effect of GnRH antagonists on menstrual cycle

The effects of the GnRH antagonist on menstrual bleeding were assessed over 12 months using an electronic daily diary. The treatment produced a dose-dependent decrease in the average number of bleeding and spotting days, as well as in bleeding intensity among those who experienced menstrual bleeding. After discontinuation, menstruation resumed in 77% of patients within 1 month and in > 95% of patients by 6 months.[45]

Comparison with Leuprolide

After 6 months, hot flushes occurred in 24–48% of patients on Elagolix, mostly mild-to-moderate in severity, compared with up to 84% in those treated with Leuprolide.[29]

Elagolix demonstrated dose- and duration-dependent BMD loss. After 6 months of treatment in Phase III studies, the mean reduction in lumbar spine BMD ranged from −0.3% to −0.7% with 150 mg OD, and −2.5% to −2.6% with 200 mg BID.[29] The magnitude of the effect of Elagolix on BMD at each dose was

less than that observed with Leuprolide acetate (a 6.3% mean decrease in lumbar spine BMD after 12 months of Leuprolide alone).[46]

In a head-to-head study by Wang ST *et al.*, vasomotor and mood-related side effects were significantly higher with Leuprolide than with Elagolix.[47]

Hot flushes affected 64% of patients on Leuprolide, compared with 12.8% among those treated with Elagolix 150 mg and 27.7% with Elagolix 200 mg BID

Rates of depression, headache, weight gain and libido decrease were also lower with Elagolix

Even with add-back therapy, Leuprolide maintained higher rates of hot flushes compared to Elagolix (Table 4). Hot flushes occurred in 30–55% of women over 12 months—approximately 88% with Leuprolide alone and 40–55% with Leuprolide plus add-back therapy.

Table 4: Comparative analysis of Elagolix and Leuprolide regimes[46]

Adverse events	Elagolix 150 mg OD	Elagolix 200 mg BID	Leuprolide	Leuprolide + NETA
Breast pain	0.2%	0.3%	3.0%	4.8%
Depression	1.3%	2.8%	12.8%	17.5%
Headache	6.8%	9.0%	22.3%	27.6%
Libido decrease	1.4%	2.8%	5.7%	3.2%
Hot flushes	12.8%	27.7%	64.1%	41.7%
Nausea	5.4%	6.7%	8.2%	9.0%
Weight gain	1.2%	1.2%	6.7%	3.5%
Breast pain	0.2%	0.3%	3.0%	4.8%

Contraindications

Elagolix is contraindicated in women who are pregnant, have known osteoporosis or have severe hepatic impairment (Child-Pugh C). It should be avoided in patients taking strong OATP1B1 inhibitors (e.g., Cyclosporine, Gemfibrozil). It is also not recommended in patients with a history of non-response to GnRH agonists/antagonists.[29]

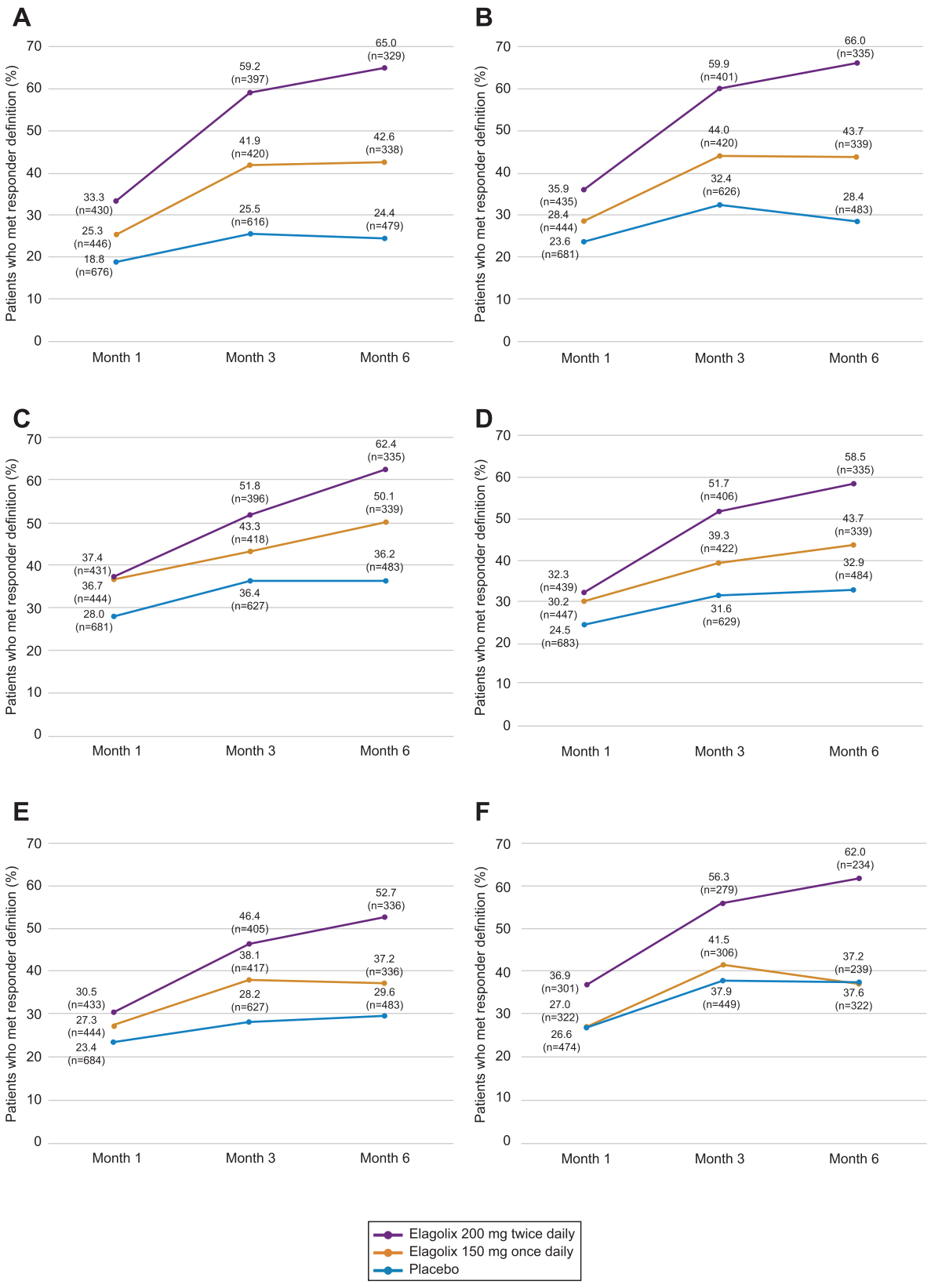
The benefits of Elagolix beyond pain

Endometriosis is increasingly recognised as a systemic condition, with effects extending beyond pelvic pain and involving multiple organ systems. These include alterations in inflammatory, immune and metabolic functions, which can lead to non-pain symptoms such as fatigue, bowel issues, weight changes, allergies and systemic inflammation. These non-pelvic manifestations can significantly affect patients' lives, with fatigue being particularly common. Endometriosis also impacts health-related quality of life and imposes a substantial economic burden, including decreased productivity at work and home.[48]

Improvement in quality of life

In addition to pain relief, Elagolix has been shown to improve disease-specific quality of life (QoL). In clinical trials, patients receiving Elagolix reported significant improvements in EHP questionnaires. The 150 mg dose significantly improved 3 of 6 EHP-30 domains at 3 and 6 months versus placebo, while 200 mg improved all six domains (pain, control and powerlessness, social support, emotional well-being, self-image and work) (Figure 10).[49]

Figure 10: Proportion of patients achieving responder status on EHP-30 subscales: A. Pain; B. Control/powerlessness; C. Emotional well-being; D. Social support; E. Self-image; F. Sexual intercourse at months 1, 3 and 6 of treatment



. (Adapted from: Taylor HS *et al. Obstet Gynecol.* 2020;136(3):501-9.)[49]

At 12 months, both doses led to across-the-board QoL improvements compared to baseline.[49]

Similarly, Pokrzywinski *et al.*[34] showed that dysmenorrhoea and NMPP responders (vs. non-responders) experienced significantly better health-related QoL and less work absenteeism.[50]

Role in adenomyosis

Similar to endometriosis, uterine adenomyosis is also an oestrogen-dependent condition and causes dysmenorrhoea and heavy menstrual bleeding (HMB).[51]

In a randomised controlled trial of 58 women with adenomyosis and infertility, Elagolix has shown improvements in primary outcomes compared to Dienogest.[51]

Women treated with Elagolix 200 mg OD for 3 months showed greater improvements than those on Dienogest (Table 5).

Table 5: Key outcomes with Elagolix 200 mg OD for 3 months vs. Dienogest

Parameter	Elagolix (200 mg OD, 3 months)	Dienogest
Pain relief (VAS score)	6.25 ± 1.83	4.84 ± 1.56
Uterine volume reduction	5.1	1.2
Haemoglobin improvement (g/dL)	−1.21 ± 0.97	−0.20 ± 0.56
Heavy menstrual bleeding (%)	3.7%	23.1%
Side effects	Fewer irregular bleeding, less weight gain	More frequent

VAS: Visual Analogue Scale.

Elagolix offered both better efficacy and a more favourable safety profile for reproductive-age women.[51]

Role in uterine fibroids

Multiple clinical trials have confirmed the role of Elagolix in reducing HMB and improving related outcomes in women with uterine fibroids.[52-55]

Phase IV randomised trial (n=82, 6 months)[52]	49.4% of women receiving Elagolix 150 mg OD met the composite bleeding endpoint vs. 23.3% on placebo
	Benefit seen as early as month 1 and sustained through month 6
	Marked improvement in bleeding suppression, haemoglobin and QoL scores
Phase IIa proof-of-concept (n=271, 3 months)[53]	Up to 98% reduction in menstrual blood loss (MBL) with highest-dose Elagolix
	Majority reached the dual endpoint (MBL <80 mL + ≥50% reduction)
	Amenorrhoea was most common at higher doses; haemoglobin increased significantly

Pooled analysis of 2 Phase III (n=126 patient with uterine fibroids and adenomyosis, 6 months)[54]	82% on Elagolix monotherapy vs. 12% on placebo achieved primary endpoint
	Uterine volume dropped by −109.4 cm³ (monotherapy) vs. +65.7 cm³ with placebo
	Bleeding suppression in 82% and significant health related QoL gains
Phase IIb trial (n=567, 6 months)[55]	Response rates: 92% with Elagolix 300 mg BID, 79–85% with add-back, vs. 27% with placebo
	MBL reduction 71–93% in Elagolix groups vs. 24% placebo
	Greater haemoglobin rise and reduction in fibroid size, especially with monotherapy

Across multiple trials, Elagolix has consistently shown it can reduce heavy bleeding, reduce the size of uterine fibroids, improve anaemia and enhance QoL in women with adenomyosis and fibroids. Its favourable safety profile and sustained efficacy make it a strong therapeutic option for reproductive-aged women facing these conditions.[52-55]

Role in fertility and assisted reproduction

Oral Elagolix has emerged as a promising alternative to injectable GnRH antagonists in controlled ovarian stimulation. Multiple retrospective studies and meta-analyses show that Elagolix effectively suppresses ovulation, maintains embryology outcomes and simplifies *in-vitro* fertilisation (IVF) protocols, reducing the need for daily injections.[56-60]

Study	Population	Dose	Key outcomes
Retrospective cohort[56]	75 women (Elagolix) vs. 75 (Ganirelix)	Oral, 200 mg	No premature ovulation; total and mature oocytes, fertilisation and blastocyst development were comparable; simplified oral administration
Systematic review and meta-analysis[57]	813 women (452 oral, 294 injectable)	Oral, 50 mg every other day; 200 mg OD/BID	Comparable cycle cancellation and fertilisation rates; oral option less invasive and cost-effective
Retrospective cohort[58]	194 patients (71 Elagolix, 123 Ganirelix)	Oral, 50 mg	Effective LH suppression and E2 rise; 1 breakthrough ovulation per group; frozen embryo transfers showed higher biochemical pregnancy rates with Elagolix
Retrospective cohort[59]	269 women (<42 years; good ovarian reserve)	Oral, 50 mg OD	Oral Elagolix was as effective as injectable GnRH antagonists in suppressing ovulation, maintaining comparable embryology outcomes and simplifying donor cycles with less frequent, lower-dose administration
Quasi-experimental[60]	60 women	Oral, 150 mg OD	E2 and lower LH; no premature luteal surge or luteinisation; pregnancy rate was slightly lower

Across multiple studies, oral Elagolix demonstrates reliable ovulation suppression, comparable fertilisation and embryo outcomes and the added advantages of convenience, fewer injections and cost-effectiveness. These results support its potential as a practical alternative to injectable GnRH antagonists in IVF protocols.[56-60]

An ongoing clinical trial, PREGNANT (pre-IVF treatment with a GnRH antagonist in women with endometriosis), is evaluating whether pretreatment with oral Elagolix can improve IVF outcomes in women affected by endometriosis.[61]

This multicentre, double-blind trial enrolled 814 women with endometriosis undergoing IVF. Elagolix 200 mg BID for 8 weeks is compared with placebo, with live birth as the primary endpoint and embryo outcomes plus obstetric complications as secondary endpoints.

Results from this trial will clarify whether oral Elagolix pretreatment can enhance fertility outcomes and pregnancy success in women with endometriosis.[61]

Take-away

- Endometriosis affects nearly 10% of women of reproductive age, and its prevalence rises to around 50% among women with infertility; often presenting with chronic pelvic pain and subfertility
- Traditional therapies (NSAIDs, OCPs, progestins, GnRH agonists and surgery) often relieve symptoms but have certain limitations.
- As endometriosis is a chronic and recurrent condition, its management requires long-term therapy; therefore, pharmacological treatments should demonstrate sustained efficacy and an acceptable safety profile for prolonged use
- Elagolix is the first oral GnRH antagonist for management of moderate-to-severe endometriosis associated pain. It competitively blocks pituitary GnRH receptors, causing rapid, dose-dependent suppression of oestrogen
- **Partial estrogen suppression:** Elagolix 150 mg maintains serum estradiol levels (42 pg/mL) within the effective and bone-safe range of approximately 30–50 pg/mL, allowing for long-term use (up to 24 months) without significant hypoestrogenic adverse effects and without the need for add-back therapy. Elagolix 200mg BID offers complete estrogen suppression (12 pg/mL) required for conditions like severe dysmenorrhea, non-menstrual pelvic pain, dyspareunia, deep infiltrating endometriosis and can be used for 6 months continuously
- **Efficacy:** Both 150 mg OD and 200 mg BID significantly reduce dysmenorrhoea and non-menstrual pain versus placebo, with sustained relief for up to 12 months post treatment discontinuation
- Systematic review & network meta-analysis: Elagolix offers greater relief from dysmenorrhoea than other interventions, including injectable GnRH antagonists, Injectable GnRH agonists, progestins and COCs, and Elagolix monotherapy provides better improvement in dyspareunia as compared to GnRH analogues with add-back therapy
- Elagolix is generally well tolerated, lower incidence of break-through bleeding with mild, dose-dependent adverse effects such as hot flushes and headache. It has minimal, dose-dependent effects on bone mineral density (BMD), which are typically reversible upon discontinuation of therapy. No new safety signals emerged in long-term studies
- **Beyond pain:** Elagolix improves quality of life score in endometriosis patients (EHP-30 scores). It is also effective for controlling heavy menstrual bleeding associated with fibroids and may benefit in patients with adenomyosis. It has role for prevention of premature LH surge in patients undergoing ART.
- **Clinical use:** Elagolix may be considered as an emerging, potential first-line therapy for patients with moderate-to-severe endometriosis-associated pain
- **Indian Experience (Phase-III study):** Elagolix shows similar effectiveness to Dienogest in symptom management but with fewer adverse events and less impact on BMD, positioning it as a safer option for the management of endometriosis-associated pain
- **In conclusion, Elagolix can be considered as an emerging, potential first-line therapeutic approach in the management of endometriosis**

Abbreviations: AAFP: American Academy of Family Physicians; CNGOF: Collège National des Gynécologues et Obstétriciens Français; COC: Combined oral contraceptive; E2: Oestradiol; EHP: Endometriosis Health Profile; ELARIS EM: Endometriosis; ER: Oestrogen receptor; ESHRE: European Society of Human Reproduction and Embryology; GnRH: Gonadotropin-releasing hormone; LNG-IUS: Levonorgestrel intrauterine system; NSAID: Non-steroidal anti-inflammatory drug; OATP: Organic anion-transporting polypeptide; OCP: Oral contraceptive pill; OD: Once daily; PGIC: Patient Global Impression of Change; BID: Twice daily; WHO: World Health Organization

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