ELAGOLIX (ORILISSA)

By: Cindy Lu

https://www.orilissa.com/cost

Background

- First described in the literature in 2005
- Originally developed by Neurocrine Biosciences
  - Later Abbott Laboratories (AbbVie, Inc)
- 2010: global agreement to develop and commercialize Elagolix for endometriosis treatment
- Phase III clinical trials completed in 2016
- September 2017: AbbVie filed New Drug Application (NDA)
- First new medication to be approved by FDA for endometriosis treatment in a decade
- First oral treatment for pain management of endometriosis

About Orilissa

- Brand name: Orilissa
- Generic name: Elagolix
- Drug class: Gonadotropin-releasing hormone antagonist
  - Bind to gonadotropin-releasing hormone to suppress the secretion of hormones
- Company: AbbVie, Inc
- Date approved: July 23, 2018

AbbVie Inc.

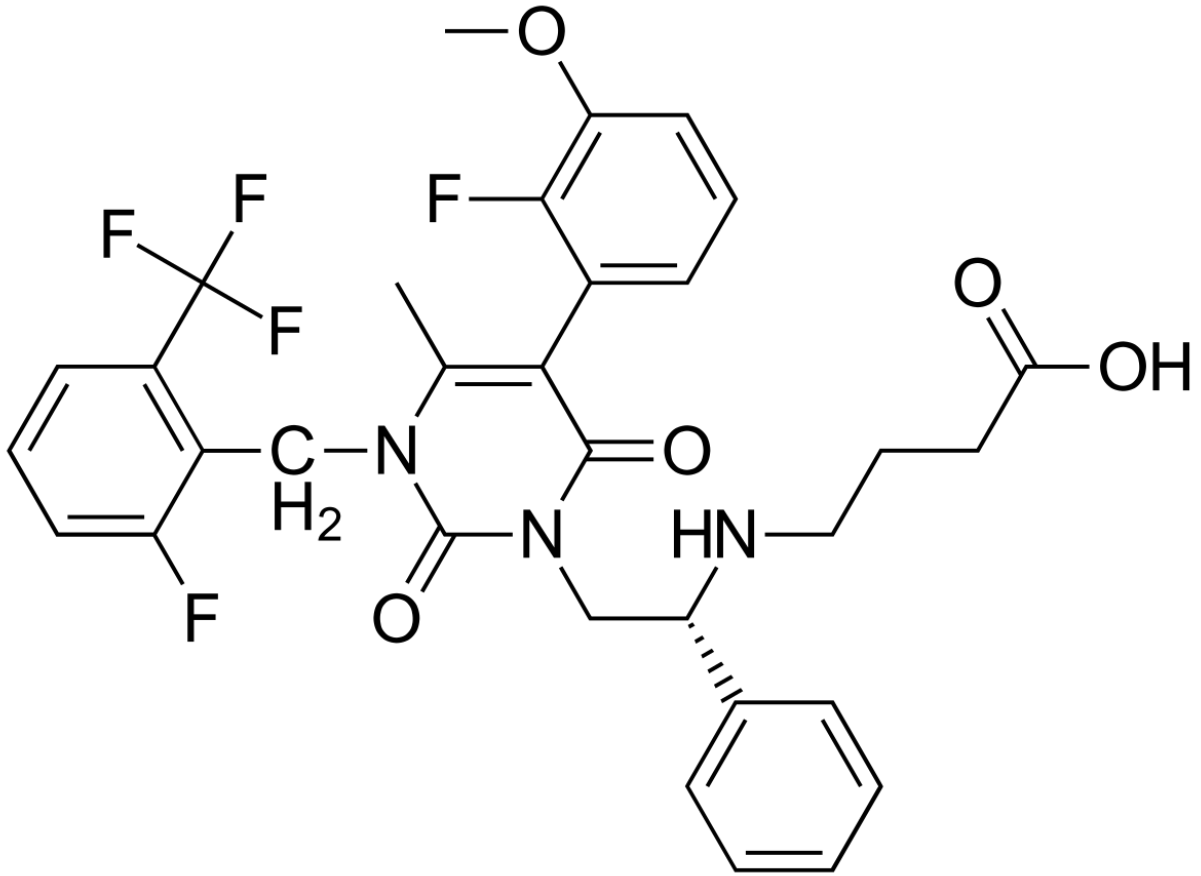
- Pharmaceutical company founded in 2013
- Products:
  - Humira: treats autoimmune diseases
  - Imbruvica: treats mantle cell lymphoma and other cancers
  - Venclexta: treats chronic lymphocytic leukemia
  - Norvir: treats HIV/AIDS
- Committed to drug development in the cystic fibrosis disease area since 2019

Elagolix Chemical Properties

$C_{32}H_{30}F_5N_3O_5$

Water solubility : 0.00243 mg/mL

- Molar Mass: 631.6 g/mol
- Hydrogen bond donor count = 2
- Hydrogen bond accepter count = 11
- Formal Charge = 0
- Double bonds = 13
- Single bonds = 34
- 3 homocyclic ring, 1 heterocyclic ring
- Has lots of possibility for hydrogen bonding



https://en.wikipedia.org/wiki/Elagolix

Elagolix is used in women with endometriosis

- Endometriosis: condition where tissue that normally lines the inside of the uterus grows outside of the uterus
  - Causes tissue that should be shed every month to grow on other organs
    - ovaries, fallopian tubes, and bladder
      - May stick together and cause inflammation and pain
  - Results in pain during periods and intercourse, increase rates of cancer and infertility
- Affects 10 % of women of reproductive age
- Is prescribed if hormonal birth control and nonsteroidal anti-inflammatory drugs (NSAIDs) don't work

Endometriosis

- The cause is not known, but possible explanations could be:
  - **Retrograde menstruatio**n: blood (contains endometrial cells) flow back through fallopian tubes, into the pelvic cavity instead of out of the body
  - **Transformation of peritoneal cells:** peritoneal (abdomen) cells are transformed into endometrial-like cells by hormones or immune factors
  - **Embryonic cell transformation:** hormones transform embryonic cells into endometrial-like cells during puberty
  - **Surgical scar implant:** post-surgery incision endometrial cells can attach to
  - **Immune system disorder:** prevents the recognition and destruction of endometrial-like tissue that grows

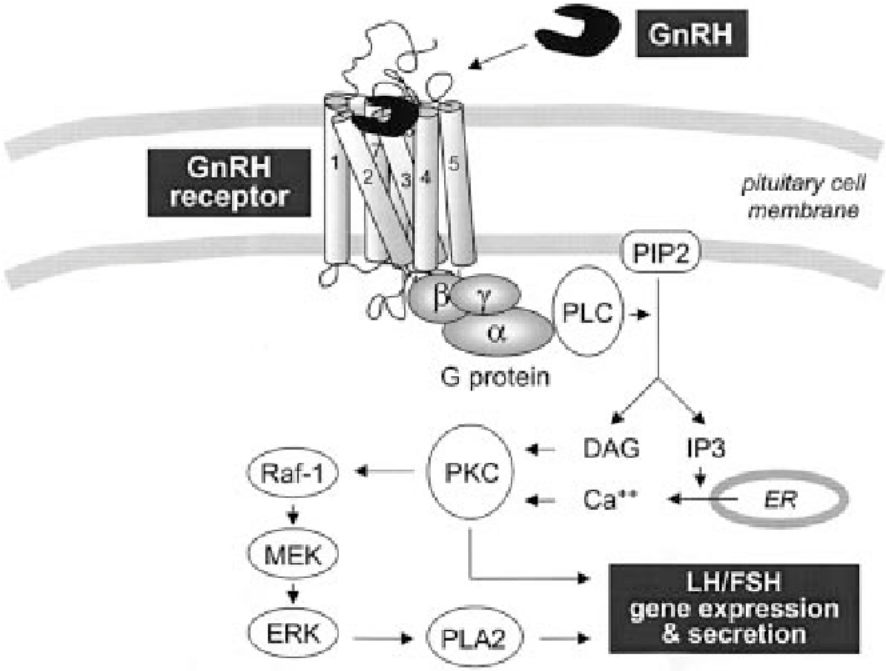
Endometriosis cont.

- Risk of developing endometriosis increases if:
  - Menstrual cycle start at an early age/Menopause starts at an older age
  - Had first child older than 35
  - Having high levels of estrogen
  - Genetics/family history
  - Born with a narrow cervix
  - Have a low body mass index

Mechanism of Action

- Orally administered small molecule (nonpeptide)
- Acts on the gonadotropin-releasing hormone (GnRH) receptor located in the pituitary gland
  - G-protein coupled receptor that regulates reproduction
  - Binds proteins (GnRH)
  - Antagonist binds competitively causing less GnRH binding
    - Decreased secretion of LH and FSH
- Equilibrium dissociation constant (Kd) = 54 pM (highly potent)
  - affinity of elagolix for the GnRH receptor

Normal function of GnRH receptor



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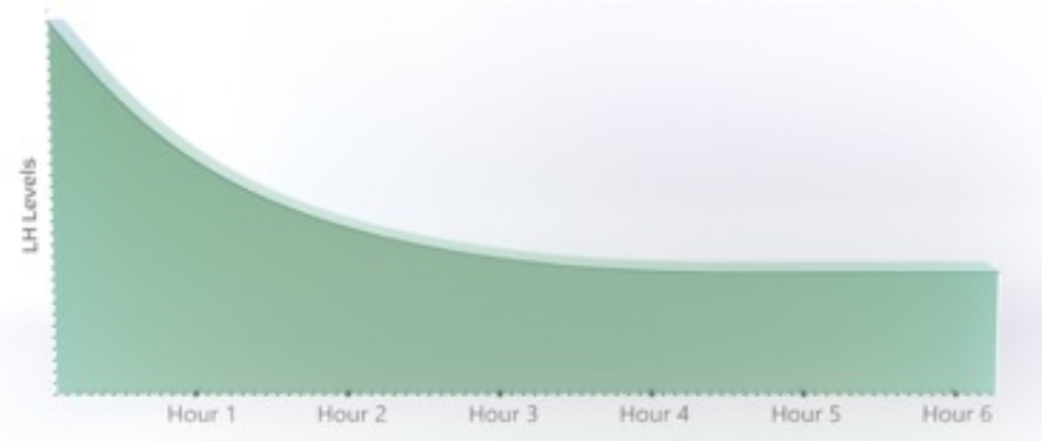
Elagolix decreases the release of two hormones

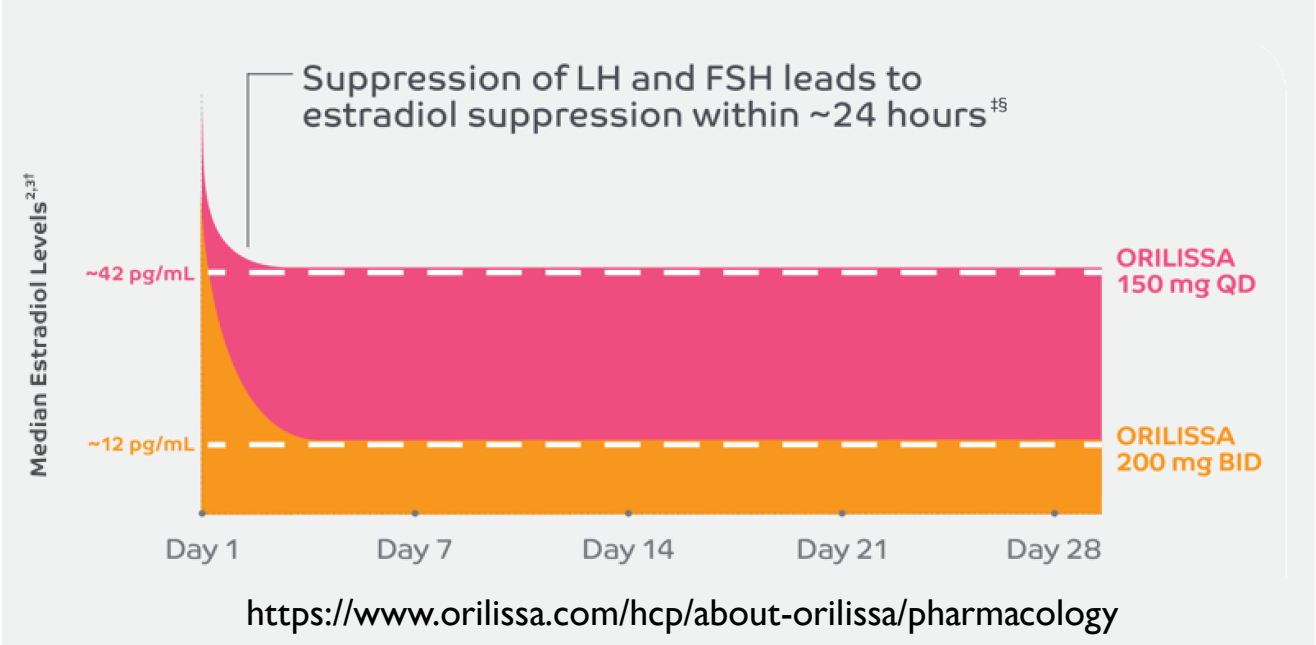


- Suppresses 2 hormones produced in the pituitary gland
  - **Follicle-stimulating hormone(FSH):** stimulates the ovarian follicle which causes an egg to grow in the ovaries and triggers the production of estrogen
  - **Luteinizing hormone (LH):** induces the release of the egg from the ovary (ovulation)
- Dose dependent after 4-6 hours after administration

https://www.orilissa.com/hcp/about-orilissa/pharmacology

Elagolix also causes decrease in estrogen levels

- Menstrual cycle increases production of estrogen hormones in the body
- Estradiol (a form of estrogen) regulates the growth of uterine tissue
  - in endometriosis the tissue is grown outside the uterus causing pain and inflammation
- Suppression of estradiol is dose dependent
  - 150 mg: ~42 pg/mL
  - 200 mg: ~12 pg/mL
- Occurs quickly, within ~24 hours
- Returns to baseline ~24-48 hours after discontinuation



https://www.orilissa.com/hcp/about-orilissa/pharmacology

Pharmacology

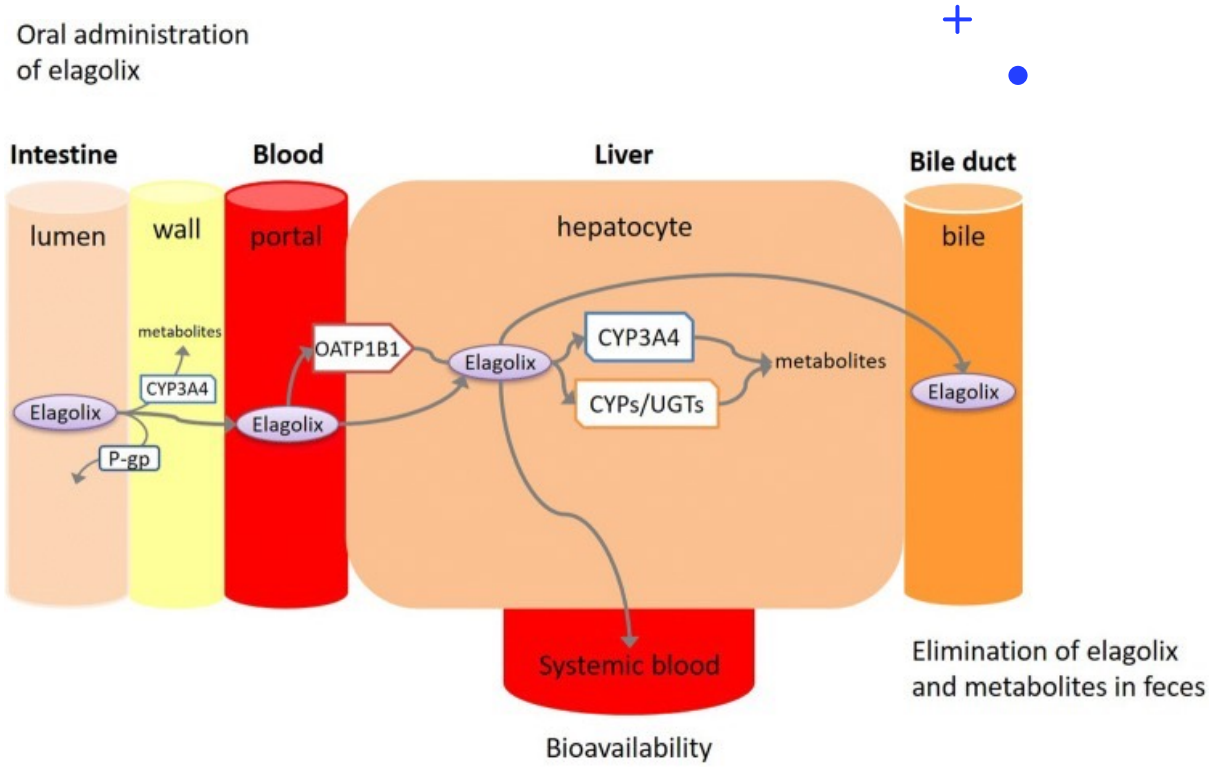
- Route of Administration: oral tablets
  - 150 mg once per day for 24 months
  - 200 mg twice per day for 6 months
- It takes 1 hr to reach the maximum drug concentration (Cmax) in the body (Tmax)
- Cmax for 150 mg has a mean of 574 ng/mL
- Cmax for 200 mg has a mean of 744 ng/mL
- No clinically relavent prolongation of QTc interval

Pharmacology cont. (pharmacokinetics)

Pharmacokinetic factors	150 mg (once daily)	200 mg (twice daily)
R_{ac} = drug acculation	0.98	0.89
AUC = area under plasma concentration-time curve	1292 ng*hr/mL	1725 ng*hr/mL
AUC/dose	8.61 ng*hr/mL	8.62 ng*hr/mL
CL/F = oral clearance	123 L/hr	144 L/hr
Vss/F = apparent volume of distribution at steady rate	1674 L	881 L
C_{max}/dose	3.83 ng/mL	3.87 ng/mL

Metabolism of elagolix

- Metabolized by CYP3A by hepatic metabolism (liver)
  - Average half life of 4.29 hrs for 200 mg
  - Average half life of 6.42 hrs for 150 mg
- Not significantly impacted by food (may be taken with or without food)
  - All phase III studies were similar regardless pf drug administration with respect to meals
- 69% of the administered dose was recovered in feces and urine as metabolites
  - 90.1% in feces
  - 2.9% in urine



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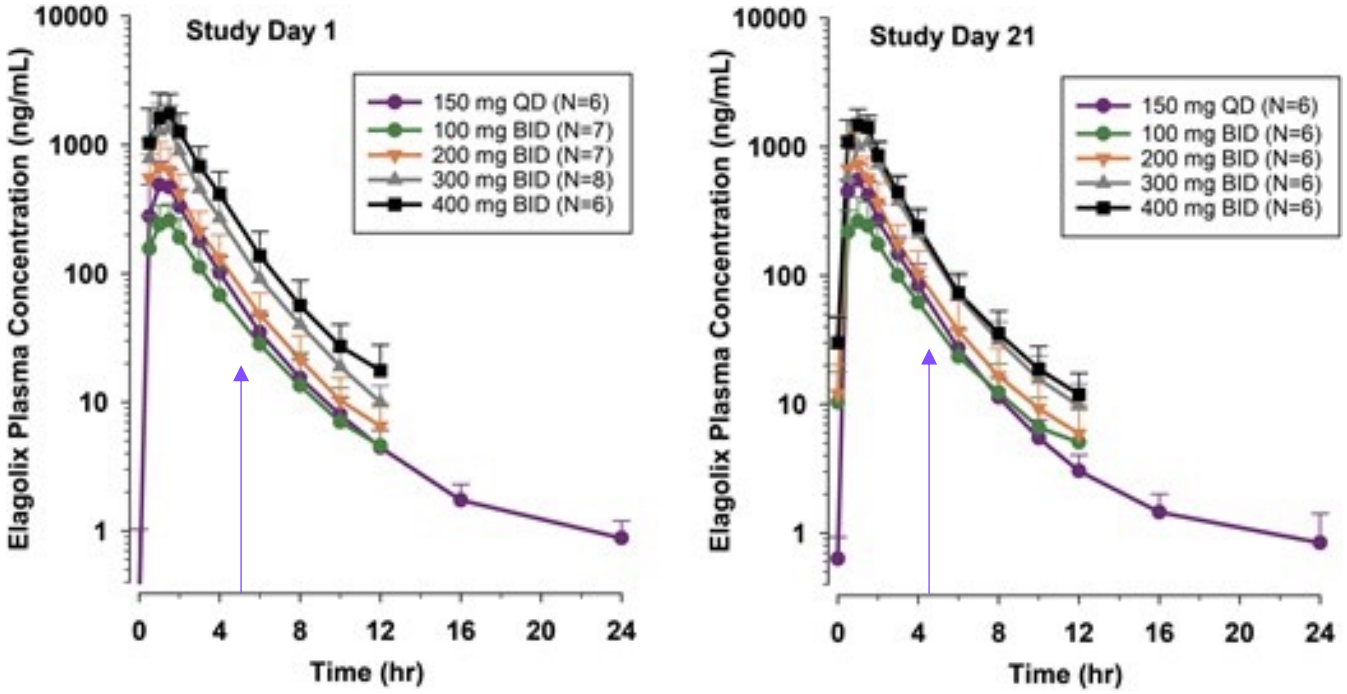
Elimination Rate Processes



Elagolix plasma concentration-time profiles on day 1 and 21

https://academic.oup.com/jcem/article/102/5/1683/3001063

- Biphasic elimination
- 93% of dose recovered approximately 9 days after dosing
  - 90% in feces
  - <3% in urine
- Half life ($t_{1/2}$) = 4-6 hrs
- R_{ac} (drug accumulation) <1
  - Little to no accumulation was observed
- Confirms dose proportionality

Elagolix is considered after 2 other methods have failed

- Elagolix is prescribed when nonsteroidal anti-inflammatory drugs (NSAID) and hormonal birth control has failed
  - NSAIDs: class of medicines that are used to relieve pain, decrease inflammation, decrease fevers, and prevent blood clots
    - Enzyme inhibitor
  - Hormonal birth control: inhibits the release of eggs from the ovaries by suppressing LH

Possible Dosing

- 2 main options:
  - 150 mg once per day
    - 24 months
    - Recommended for patients with no coexisting conditions
  - 200 mg twice per day
    - 6 months
    - Recommended for patients with dyspareunia
    - Stronger strength
- If patient has hepatic impairment:
  - 150 mg once per day for 6 months

Toxicity

- Common adverse reactions:
  - Hot flush
  - Headache
  - Nausea
  - Insomnia
  - Depression
  - Anxiety
  - Bone loss (dose dependent decrease in bone mineral density)
  - Changes in menstrual bleeding patterns

- Serum enzyme elevations: can diagnose liver dysfunction
  - No published reports of clinically apparent liver injury with use of Elagolix

Contraindications

- Contraindicated in women who
  - Are pregnant
    - May cause miscarriage
  - have/are predisposed to osteoporosis
    - Causes loss in bone density
  - Have severe hepatic (liver) impairment
  - Are taking inhibitors of organic anion transporting polypeptide
  - Have hypersensitivity reactions to ORILISSA

Post marketing Surveillance

- Post marketing surveillance is still in progress, currently at around Phase IV, most Phase I-III clinical trials have been completed, some however, are still recruiting/active.
- Phase I: 2 (1 complete, 1 recruiting)
- Phase II: 10 (8 complete, 2 recruiting)
- Phase III: 13 (8 complete, 2 recruiting, 2 active, 1 terminated)
- Phase IV: (1 recruiting, 1 unknown)
- Currently no MedWatch entries

Phase I Clinical Trials

- June 2011-November 2012
- 216 participants
  - Criteria: women who are 18-40 years old with a history of regular menstrual cycles and FSH levels <35 mIU/mL
- Studies Elagolix dosing on ovarian activity and ovulation in healthy premenopausal females
- Results were not posted
- Phase I clinical trial in Ireland concluded reduction of estradiol, stop in vaginal bleeding, absence of ovulation, with some side effects (ex. hot flushes), and not excessive adverse impact on bone marrow density (BMD)
  - Concluded add back therapy was not needed

Add back therapy for endometriosis

- Study on endometriosis and add-back therapy conducted in 2004 shows:
  - GnRH analogues: suppresses ovulation and creates a temporary state of menopause
    - Treatment is limited to 6 months due to possible complications with hypoestrogenism (osteoporosis)
  - Add back therapy refers to supplementing treatment with estrogen or progestogen to fight hypoestrogenism
  - Indications that there was no difference in bone loss in women who were treated with add-back therapy and those treated without
  - Outcomes: add-back therapy and oral contraceptive groups had similar bone densities after a 6 month follow up, absence of add back however, showed results of bone density significantly lower than the groups add back and oral contraceptives.

Phase II Clinical Trials

Clinical Trial 1 (3 months)

- Two treatments: 150 mg once a day or 200 mg twice a day
- Response variable: precent reported reduced period pain (dysmenorrhea) and percent reported reduced pelvic pain between periods

	Trial 1		
	ORILISSA		Placebo
	150 mg once daily N=248	200 mg twice daily N=244	N=373
Dysmenorrhea Difference from placebo	46% 27%**	76% 56%**	20%
Non-Menstrual Pelvic Pain Difference from placebo	50% 14%**	55% 18%**	36%

Demographics

- all women study
- Majority race was white
- Age ranges from 18-49
  - works similarly
- Double blind experiment

https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-orilissa

Phase II Clinical Trials cont.

Clinical Trial 2 (3 months)

- Same test
- Similar results as Clinical trial 1

Safety and Efficacy Study

- 150 mg once a day vs. placebo in an 8-week double blind experiment
- Observes pain during daily activities at weeks 4 and 8
- Observes intercourse pain at weeks 4 and 8
- Observes result of non-menstrual pelvic pain score at weeks 4, 8, 12, 16, 20, 24, and 30 (6 weeks posttreatment)
- Outcome: Supports the cause of symptoms like nausea, hot flushes, and headaches

	Trial 2		
	ORILISSA		Placebo
	150 mg once daily N=221	200 mg twice daily N=225	N=353
Dysmenorrhea Difference from placebo	43% 21%**	72% 50%**	23%
Non-Menstrual Pelvic Pain Difference from placebo	50% 13%**	58% 21%**	37%

https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-orilissa

Phase III Clinical Trials

- Studies that evaluates global safety and efficacy of Elagolix in subjects with moderate to severe endometriosis-associated pian
  - Participants from Argentina, Austria, Australia, Brazil, Czech Republic, Hungary, Italy, New Zealand, Poland, South Africa, Spain, US, and UK
  - Placebo vs. 150 mg vs. 200 mg
  - Treatment period 3 months
  - Measured in P values and specified that "For an Elagolix dose group to be considered statistically significantly better than placebo on a secondary endpoint, the P value must have been ≤ 0.025"
    - All P values are satisfactory
  - Most adverse events include symptoms of taking Orilissa (hot flushes, headache, nausea, urinary tract infection, etc.)

Phase III Clinical Trials cont.

- Studies that evaluates safety and efficacy of Elagolix use with Estradiol and Norethindrone Acetate to manage heavy menstrual blood flow
  - Hormonal birth control pills
  - Studied placebo vs. 150mg vs. 200 mg in a 1:1:2 ratio
  - Measures final month vs initial month for up to 6 months
  - Also evaluates effect of hemoglobin on treated subjects
  - Adverse events are symptoms of taking Orilissa (hot flushes, headaches, nausea, etc.)
  - Outcomes: using Elagolix with norethindrone did not show reduction in plasma concentration of norethindrone

Phase III Clinical Trials cont.

- Studies that assess dysmenorrhea when Elagolix is used with oral contraceptives (active/recruiting)
  - Estimated completion date (April 4, 2026)
  - Participants will receive elagolix or placebo tablets along with combined oral contraceptive (COC) or placebo capsules for 3 months.
  - Participants will attend regular visits during the course of the study at a hospital or clinic, effects of the treatment will be checked by medical assessments, blood tests, checking for side effects, and completing questionnaires

Phase IV Clinical Trials

- Study with a goal to determine if treatment with Elagolix will improve body weight, waist circumference, muscle strength, cortisol secretion, blood glucose, cholesterol, and bone quality as well as mood and quality of life in a female patient with mild hypercortisolism
- Cortisol: a hormone normally made by the adrenal glands- even mild elevations in cortisol levels can negatively impact blood glucose levels, serum cholesterol levels, weight and other metabolic parameters.
  - This can lead to an increase in risk for cardiovascular disease
- Elagolix might be an effective treatment for post-menopausal females with mild hypercortisolism.
  - Growth of adrenal adenomas is thought to be driven by sex hormones affected endometriosis

Bone Mineral Density Loss (Osteoporosis risk)

- Low estrogen level causes bone mineral density loss
- Impact of loss in bone mineral density on long term bone health and fracture risks are unknown
- May not completely recover after Elagolix treatment
- Measures for prevention:
  - Vitamin D supplements
  - Calcium supplements
- Should not use Elagolix if you have a broken bone

Overdose/Missed dose

- If dose is missed: take the dose later in the day, otherwise, skip the missed dose and return to normal schedule
- Do not take two doses, can cause overdose

- Overdose increases risk of side effects
- Symptoms of overdose:
  - Nausea
  - Headache
  - Hot flashes
  - Anxiety
  - Dizziness
  - Irritability

Cost/Worth evaluations

- $845 every four weeks (without insurance)
- Annual price = ~$10,140
- No generic form available, only brand
- “The Institute for Clinical and Economic Review (ICER) issued an affordability and access alert, At Orilissa's current price, only a quarter of eligible patients could get the drug without exceeding ICER’s healthcare burden threshold”
  - Compared to no treatment at all, the cost does not exceed the upper limit
- Endometriosis surgery canbe as low as $10,000
  - Finite surgery: complete surgery completely removes endometriosis, incomplete surgery/no surgery, endometriosis continues
- Should not be first option

Frequently Asked Questions

- How long does ORILISSA take to work?
  - 24 hours; however, pain relief will take longer
  - may take 3 months to experience the full benefits of endometriosis pain relief
- What types of birth control should I use with ORILISSA?
  - ORILISSA does not prevent pregnancy
  - effective methods can include condoms or spermicide
  - Birth control pills that contain estrogen may make ORILISSA less effective
- How should ORILISSA be stored?
  - Stored between 36°F – 86°F, out of reach from children
- Can I breastfeed while taking ORILISSA?
  - Impact on breastmilk and the nursing baby is unknown

Goal of drug development/further uses

- Elagolix has been used in trials studying
  - treatment of **Endometriosis**
  - **Folliculogenesis**: the maturation of the ovarian follicle (dense mass of somatic cells that form an immature oocyte)
  - **Uterine Fibroids**: noncancerous growth of the uterus (during childbearing years)
  - Heavy **Uterine Bleeding** (not in menstrual cycle)
  - Heavy **Menstrual Bleeding**

Why did I choose Orilissa

- Happy National Women's History month!
- I encountered the condition endometriosis in a video by CUT in their Lineup series
  - Intrigued by the guesser who guessed correctly say, "I know there's not too much research about it"
- When I was looking up new drug approvals in the last 5 years, I scrolled and read the condition for which each drug was approved for and felt that "endometriosis" sounded so familiar to me
  - Wanted to do something with thalassemia or hemoglobin H disease, decided against it

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