
Elagolix for Endometriosis

Public Meeting – Afternoon Session
July 12, 2018



WIFI Network: Student
Password: [Open network]

Welcome and Introduction

Why are we here this afternoon?

[T]here is an important unmet need to treat patients with symptomatic endometriosis. With no cure or innovations for the past two decades, new diagnostic and therapeutic options have the potential to improve a woman's health status significantly and thus reduce the social and economic burdens associated with this disease, including medical expenses.

- *Society for Women's Health Research*

About 1 in 10 women suffer from endometriosis during their reproductive years, so an approval could generate annual sales well into the 9-figures. Elagolix's total market opportunity could be even bigger than that: AbbVie released positive data for the drug from the first of two uterine fibroid trials on Feb. 21, and on Tuesday, it reported positive data from the second.

- *The Motley Fool, March 13 2018*

Welcome and Introduction

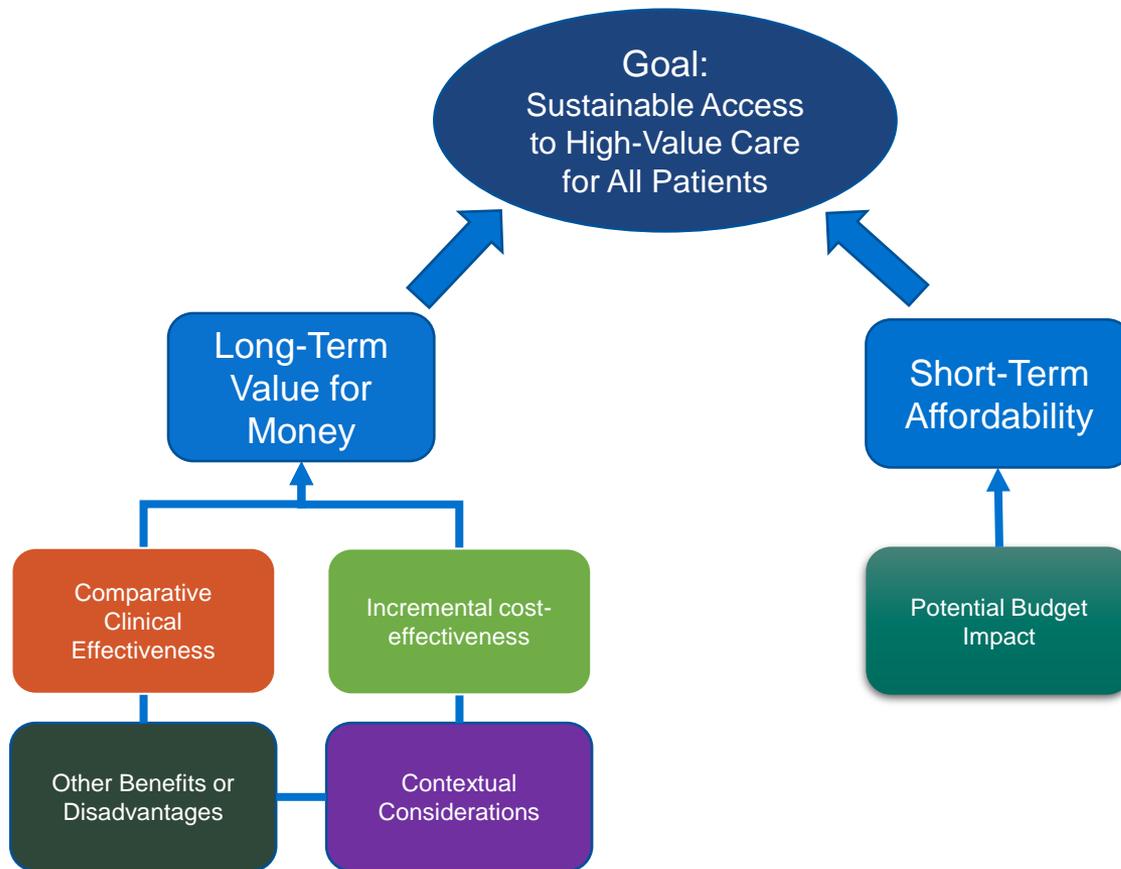
Why are we here this afternoon?

- Increasing health care costs affecting individuals, state and federal budgets
- New mechanisms of action often raise questions about appropriate use, cost
- Patients can have difficulty accessing drugs
 - Step therapy protocols
 - Requirements to switch drugs with new insurance
 - High out-of-pocket costs
- Need for objective evaluation and public discussion of the evidence on effectiveness and value

Welcome and Introduction

How was the ICER report on elagolix developed?

- Scoping with guidance from patient groups and advocates, clinical experts, manufacturers, and other stakeholders
- Internal ICER staff evidence analysis
- University of Colorado – Denver cost-effectiveness modeling
- Public comment and revision
- Expert report reviewers
 - Dr. John Petrozza, Chief, Division of Reproductive Medicine and IVF; MGH
 - Casey Berna, Endometriosis Advocate
- How is the evidence report structured to support CEPAC voting and policy discussion?



Afternoon Agenda

- 1:00 pm:** Welcome and Opening Remarks
- 1:10 pm:** Presentation of the Evidence and Economic Modeling
- Steven J. Atlas, MD, MPH, Director, Primary Care Research and Quality Improvement Network, Massachusetts General Hospital
 - R. Brett McQueen, PhD, University of Colorado - Denver
- 2:10 pm:** Public Comments
- 2:30 pm:** NE CEPAC Vote on Clinical Effectiveness and Value
- 3:15 pm:** Policy Roundtable Discussion
- 4:45 pm:** Reflections from Experts and NE CEPAC Panel
- 5:00 pm:** Meeting Adjourned

Evidence Review

Steven J. Atlas, MD, MPH

Director, Primary Care Research and Quality
Improvement Network

Massachusetts General Hospital



INSTITUTE FOR CLINICAL
AND ECONOMIC REVIEW

Key review team members:

Geri Cramer, BSN, MBA

Patricia Synnott, MALD, MS

Leslie Xiong, BS

Disclosures:

We have no conflicts of interest relevant to this report.

Topic in Context

- Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial-like tissue outside of the uterus
- Symptoms vary in severity and include painful menstrual periods (dysmenorrhea), nonmenstrual pelvic pain, pain during intercourse (dyspareunia)
- Affects 6-10% of women of reproductive age, with peak prevalence between 25 to 35 years of age
- Estimated population in the United States: 4-10 million women

Therapies for Endometriosis

- Available medical and surgical treatments can decrease symptoms, but none offer long-term relief
- Initial therapy often includes nonsteroidal anti-inflammatory drugs and hormonal contraceptives
- FDA approved gonadotropin-releasing hormone (GnRH) agonists used as a second line treatment
 - Only available by injection or intranasal administration
 - Initially stimulates pituitary gland to release female hormones and can worsen symptoms during first 2 weeks
- Elagolix is a short-acting, oral, nonpeptide, GnRH antagonist under review by FDA
 - Rapidly suppresses the pituitary-ovarian hormones and produces dose-dependent estrogen suppression

Endometriosis from a Patient Perspective

- Symptoms can affect patient's quality of life by increasing depressive symptoms, reducing sexual satisfaction, and disrupting personal relations
- Misperception that endometriosis is “bad menstrual cramps” leads to under-appreciating its impact, including work and family issues
- Lack of sufficient awareness by clinicians may account for delays in diagnosis as well as not enough research looking for new therapies
- Some patients concerned that elagolix use may end up delaying potentially beneficial surgery

Scope of the Review

- To evaluate the comparative clinical effectiveness of elagolix for symptomatic endometriosis
- Comparators:
 - Placebo (no treatment), GnRH agonists, hormonal contraceptives, aromatase inhibitors
- Key outcomes & harms

Outcomes	Harms
Dysmenorrhea	Low estrogen side effects
Nonmenstrual pelvic pain	Bone mineral density changes
Quality of life	Lipid profile changes
Use of analgesics	Congenital malformations

Body of Evidence

- Five trials of elagolix
 - 2 Phase III RCTs, 3 Phase II
 - 4/5 studies included a placebo arm
 - 2/5 included active-controls:
 - Depot medroxyprogesterone acetate (DMPA)
 - GnRH agonist: Leuprorelin acetate
- Key differences across studies
 - Dosing of elagolix
 - Populations: Time since diagnosis, BMI
 - Outcomes: choice of endpoints and method of assessment

Overview of Randomized Trials

Key Trials	Treatment Groups	Patient Characteristics	Primary Outcome
EM-I Phase III Parallel-arm RCT	Placebo Elagolix 150 QD Elagolix 200 BID	N=872 Median age: 31 BMI (kg/m ²): 28	Clinical Response
EM-II Phase III Parallel-arm RCT	Placebo Elagolix 150 QD Elagolix 200 BID	N=817 Median age: 33 BMI (kg/m ²): 27	Clinical Response
Tulip PETAL Phase II Parallel-arm RCT with crossover	Placebo Elagolix 150 QD Elagolix 250 QD Leuprorelin acetate 3.75	N=174 Mean age: 31 BMI (kg/m ²): 23	Multiple pain measures
PETAL Phase II Parallel-arm RCT	DMPA-SC Elagolix 150 QD Elagolix 75 BID	N=252 Mean age: 32 BMI (kg/m ²): 26	Change in BMD
Lilac PETAL Phase II Parallel-arm RCT	Placebo Elagolix 150 QD Elagolix 250 QD	N=155 Mean age: 31 BMI (kg/m ²): 27	Change in monthly pelvic pain

Key clinical outcomes

- **Primary Outcome:**

- Patient Reported Clinical Response (%)
 - Stable or reduced analgesic use and
 - Clinically meaningful reduction in 1) dysmenorrhea, or 2) nonmenstrual pelvic pain

- **Secondary Outcomes:**

- Single item pain questions
 - Numeric rating scale: 11-point response
 - Biberoglu and Behrman (B&B) scale: 4-point response
- Weighted average combined response for dysmenorrhea and pelvic pain: derived for CEA model
- Quality of life
 - Endometriosis Health Profile (EHP-30): 30-item with 4-point response covering 5 domains

Results

Primary Outcome: Response at 6 months

- Clinical Responders

		Dysmenorrhea (%)	Nonmenstrual Pelvic Pain (%)
EM-I	Placebo	23.1	34.9
	Elagolix 150 QD	42.1	45.7
	Elagolix 200 BID	75.3	62.1
EM-II	Placebo	25.4	40.6
	Elagolix 150 QD	46.2	51.6
	Elagolix 200 BID	76.9	62.2

Secondary Outcomes: Pain Measures

- Statistical improvements in dysmenorrhea and nonmenstrual pelvic pain scores with elagolix compared to placebo
- Weighted average combined response for dysmenorrhea and nonmenstrual pelvic pain
 - 65.6% of 200 mg BID elagolix group vs. 35.3% of placebo group
- Differences between elagolix and active comparators in Phase II trials were not significant or not tested

Key Outcomes: Quality of Life

- Significant improvement in all dimensions of EHP-30 at 3 and 6 months with 200 mg BID elagolix vs. placebo
- 3-4 dimensions improved with 150 QD elagolix vs. placebo in Phase III trials
- Statistically significant improvement with leuprorelin acetate vs. elagolix 150 QD
- No difference in quality of life between DMPA and elagolix

Harms

	Placebo	Elagolix 150 mg	Elagolix 200 mg	Leuprorelin Acetate	DMPA
Any AE leading to DC	6	4 – 6	9 - 10	4	17
Any serious AE	3	1 – 5	2 - 3	NR	4
Amenorrhea	0.3	3 – 5	6 - 9	98	NR
Headache	10 - 14	15 - 19	17 - 23	32	18
Hot flash	7 - 10	23 - 24	42 - 48	84	76
Insomnia	2 - 3	6	7 - 11	<5%	5
Mood swings	2 - 3	4 – 6	3 - 4	NR	12
Nausea	11 - 14	10 - 12	16	13	16

Other Harms

- Dose-dependent reductions in bone mineral density (BMD) at lumbar spine, femoral neck and total hip
 - 12-13% of 200 mg group lost >8% of BMD after 12 months
 - Not fully return to baseline after discontinuation
- Elevations in total cholesterol, LDL cholesterol, and triglycerides
- Safety of elagolix in pregnancy unknown
- FDA concern about liver function tests

Controversies & Uncertainties

- Differences in dosing and duration, primary endpoints, and outcome analysis across Phase II and III studies
- Elagolix vs. active comparator data from 2 Phase II studies are limited by:
 - Small sample sizes, incomplete reporting and imbalances in baseline characteristics, short duration of follow-up, high attrition, limited statistical testing
- Unable to perform quantitative indirect comparisons of elagolix regimens
- Comparative effectiveness and safety beyond 3-6 months of treatment uncertain
 - Potential long-term harms even after stopping treatment (e.g. BMD decreases persist)

ICER Evidence Ratings

Elagolix	ICER Evidence Rating
vs. Placebo	Promising but Inconclusive (P/I)
vs. GnRH agonists, hormonal contraceptives, or aromatase inhibitors	Insufficient (I)

Potential Other Benefits and Contextual Considerations

- Elagolix is first new treatment in over a decade
- Oral formulation (vs. nasal spray or intramuscular injections with GnRH agonists)
- More rapid reversal of side effects and avoids surge in hormones common with agonists
- But still works by decreased hormone level and isn't a cure for endometriosis
- Even if helpful, it is uncertain if it be used as a chronic therapy

Cost Effectiveness

R. Brett McQueen, PhD

University of Colorado Anschutz Medical Campus



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AND ECONOMIC REVIEW

Key Team Members

Melanie D. Whittington, PhD, University of Colorado

Jonathan D. Campbell, PhD, University of Colorado

Sam McGuffin, University of Colorado

Varun Kumar, MPH, MSc, Institute for Clinical and Economic Review

Rick Chapman, PhD, Institute for Clinical and Economic Review

Disclosures:

Financial support was provided to the University of Colorado from the Institute for Clinical and Economic Review.

University of Colorado researchers have no conflicts to disclose defined as more than \$10,000 in healthcare company stock or more than \$5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

Objective

Estimate the cost-effectiveness of elagolix for the treatment of endometriosis-associated pain in adult, pre-menopausal women.

Methods in Brief

Base-Case Population

Cohort Characteristic (Baseline)	Value*
Median age	32 (18-48) years
Body mass index	28 ± 6.2
Score for dysmenorrhea [0 (none) – 3 (severe)]	2.2 ± 0.5
Score for nonmenstrual pain [0 (none) – 3 (severe)]	1.6 ± 0.5
Score on numeric rating scale [0 (none) – 10 (worst)]	5.5 ± 1.7

*Weighted average of EM-I and EM-II clinical trials

Interventions and Comparators

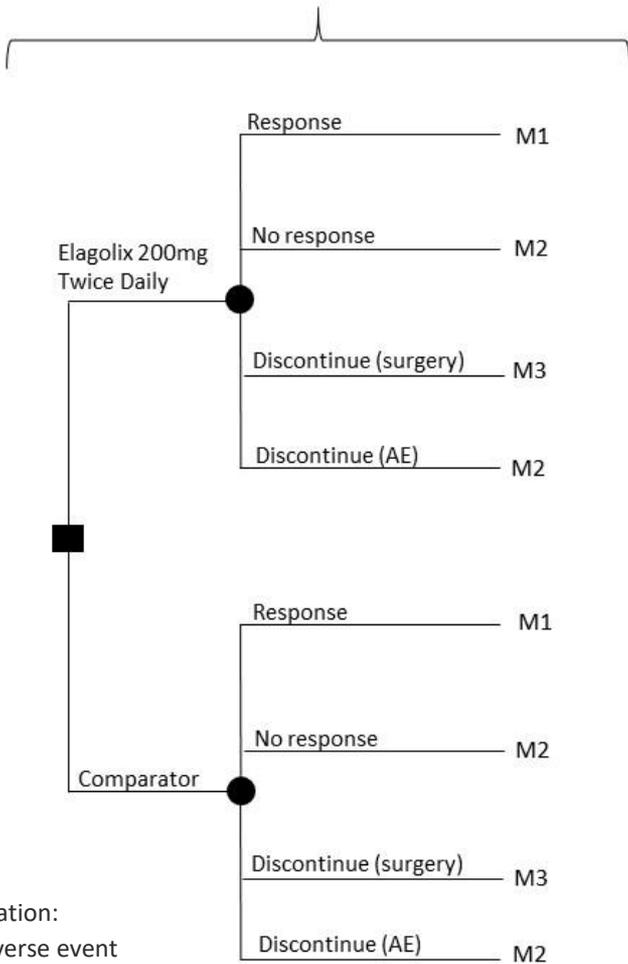
- **Intervention:** Elagolix 200mg Twice Daily
- **Primary comparator:** No active treatment or usual care (placebo with non-specific rescue analgesics)

Methods Overview

- **Model:** Decision tree & Markov model with combined dysmenorrhea and non-menstrual pelvic pain response
- **Setting:** United States
- **Perspective:** Health sector (direct medical care and drug costs)
- **Time horizon:** 18 Years (until average age of menopause)
- **Discount rate:** 3% per year (costs and outcomes)
- **Cycle Length:** 3 months
- **Primary outcome:** Cost per quality-adjusted life year (QALY) gained
- **Secondary outcome:** Surgeries, cardiovascular disease, fractures

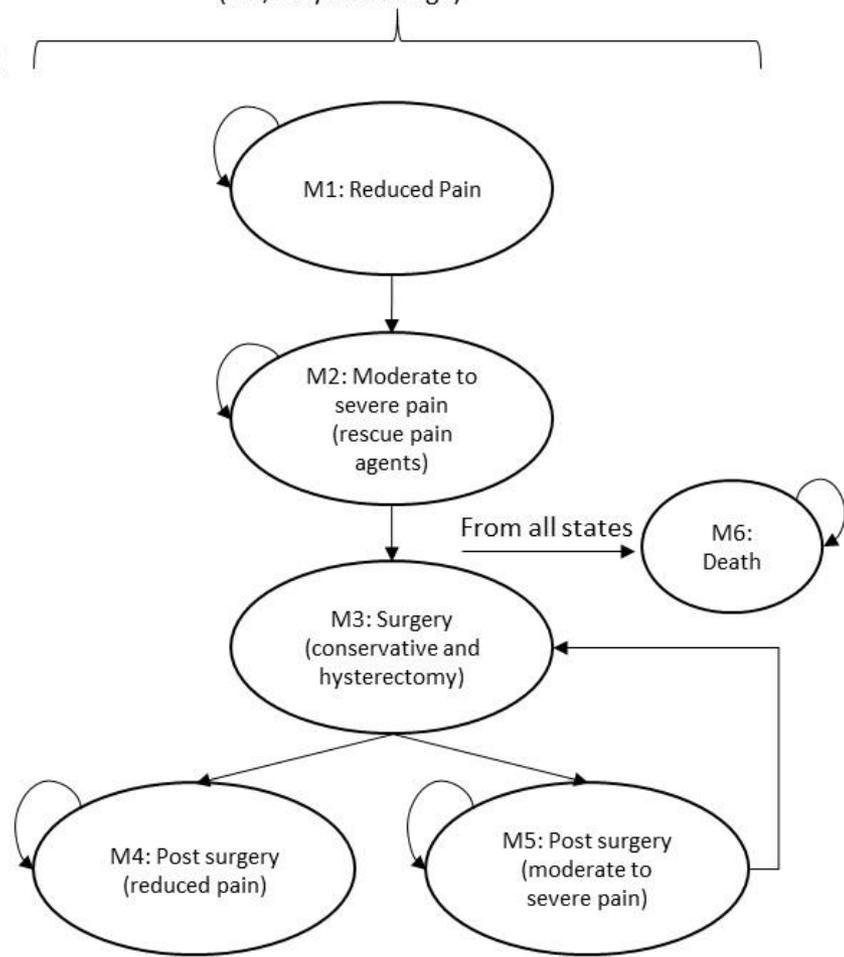
Model Schematic

Decision tree: 0-6 months – assessment of response



Abbreviation:
AE = adverse event

Markov Model: 6 months to end of model (i.e., 50 years of age)



Key Assumptions

- Short-run clinical trial evidence used to extrapolate to long-run involves assumptions on discontinuation, benefits of pain reduction, and risks from using elagolix
- Patients not responding to treatment after the first six months were not be re-treated with elagolix
- A constant proportion of women on elagolix each cycle are assumed to be off treatment for attempted and successful pregnancies
- Proportion of women in all post-surgery states incurred the cost of GnRH agonist and combined oral contraceptive add-back therapy
- Treatment acquisition price was assumed via Seeking Alpha (\$7,000 annually)

Parameters: Treatment Response Rates

	Elagolix 200mg Twice Daily	Comparator (usual care)
Response at 6 months [dysmenorrhea]	76.1%	24.2%
Response at 6 months [nonmenstrual pelvic pain]	62.1%	37.7%
Weighted average combined response (dysmenorrhea response for 5/28 days and nonmenstrual pelvic pain response for 1-5/28 days)	64.6%	35.3%
Absolute difference in weighted average response vs. placebo	29.3%	Referent

Other Key Parameters

- Pain recurrence (discontinuation due to lack of efficacy) risk ratio for elagolix vs. placebo
- Discontinuation due to adverse events and surgeries during the 6-month response assessment period for elagolix vs. placebo
- Long-run adverse events were modeled to include osteoporotic fractures and cardiovascular disease

Parameters: Health Utilities

Health State	Utility	Lower	Upper
Reduced pain health state	0.92	0.916	0.924
Moderate-to-severe pain health state	0.73	0.703	0.756
Surgical disutility (e.g., laparoscopy) for 3 months	-0.06	-0.031	-0.085
Surgical disutility (hysterectomy) for 3 months	-0.07	-0.038	0.103
Loss of fertility disutility (all subsequent post-hysterectomy health states)	-0.07	0.039	0.107

Results

Long-Run Clinical Outcomes (18 year time horizon)

Outcome (per 1,000 women)	Elagolix 200 mg Twice Daily	Comparator (usual care)	Incremental
Surgeries (e.g., laparoscopy)	368	647	-279
Surgeries (hysterectomy)	94	169	-75
Cardiovascular disease cases	16.5	15.9	0.6
Fractures	0.92	0.08	0.84

Base-Case Discounted Costs and Outcomes from Model

Intervention	Intervention Costs*	Non-Intervention Costs [§]	Total Costs	QALYs
Short-run results (6 months)[‡]				
Elagolix 200 mg twice daily [¶]	\$3,600	\$500	\$4,100	0.43
Comparator (usual care)	\$100	\$600	\$700	0.40
Long-run results (18-year time horizon)				
Elagolix 200 mg twice daily [¶]	\$61,800	\$15,500	\$77,200	11.77
Comparator (usual care)	\$6,000	\$20,000	\$26,000	11.11

*Elagolix 200 mg twice daily (not during pregnancy) over the duration of the model with addition of NSAID and opioid pain management medication vs. NSAID and opioid pain management medication alone in placebo arm

[§] Non-intervention costs include surgical costs, outpatient visits, and long-run adverse event management and treatment costs

[‡] Short-run costs and QALYs not discounted

[¶] Assumed projected price per pill = \$9.70

All costs rounded to the nearest \$100

Base-Case Discounted Incremental Results

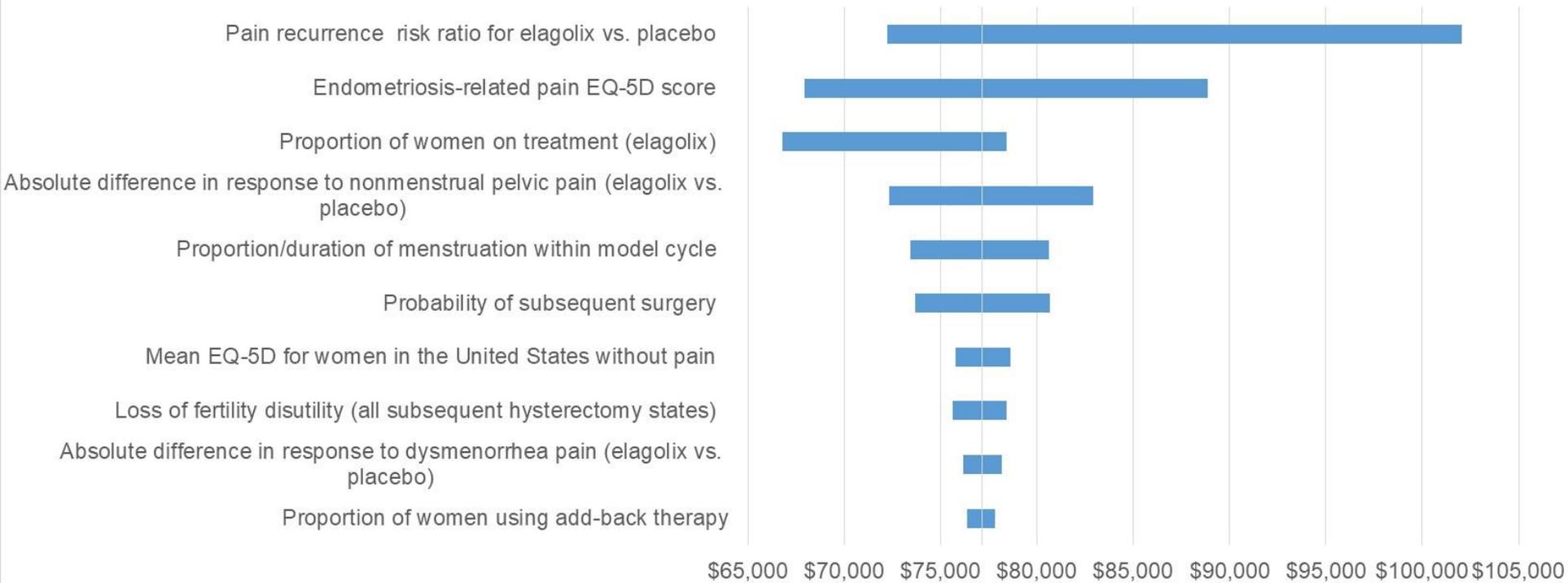
Intervention	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio (vs. comparator)
Elagolix 200 mg twice daily <i>----short-run</i>	\$3,400	0.028	\$121,000
Elagolix 200 mg twice daily <i>----long-run</i>	\$51,200	0.663	\$77,000

All costs rounded to the nearest \$100

Incremental Cost effectiveness Ratios rounded to the nearest \$1,000

Results using assumed projected price per pill of \$9.70

One-Way Sensitivity Analyses (Long-Run Time Horizon)



Base case incremental cost-effectiveness ratio: \$77,000 per QALY gained.

* The cost of the drug was not varied and was assumed at a per pill price of \$9.70 with an annual price of \$7,000.

Probabilistic Sensitivity Analysis Results

Proportion of Simulations That Were Cost-Effective			
	Cost-Effective at \$50,000 per QALY	Cost-Effective at \$100,000 per QALY	Cost-Effective at \$150,000 per QALY
Elagolix 200 mg twice daily long-run	0.26%	94.64%	99.62%

* The cost of the drug was not varied and was assumed at a per pill price of \$9.70 with an annual price of \$7,000.

Response Definition Scenario Analyses

Response definition	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio
Response to dysmenorrhea only (Elagolix 200 mg twice daily vs. placebo)	\$57,400	1.04	\$55,000
Response to nonmenstrual pelvic pain only (Elagolix 200 mg twice daily vs. placebo)	\$49,800	0.58	\$86,000
Response to both dysmenorrhea and nonmenstrual pelvic pain (Elagolix 200 mg twice daily vs. placebo)	\$43,300	0.78	\$55,000

All costs rounded to the nearest \$100

Incremental Cost effectiveness Ratios rounded to the nearest \$1,000

Incremental Results for Modified Societal Perspective (Long-Run Time Horizon)

	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio
Elagolix 200 mg twice daily vs. placebo	\$29,900	0.663	\$45,000

All costs rounded to the nearest \$100

Incremental Cost effectiveness Ratios rounded to the nearest \$1,000

Annual Threshold Price Results

Intervention	Annual Price at \$50,000 per QALY	Annual Price at \$100,000 per QALY	Annual Price at \$150,000 per QALY
Elagolix 200 mg twice daily short-run*	\$2,900	\$5,800	\$8,400
Elagolix 200 mg twice daily long-run	\$4,700	\$8,800	\$12,800

*Represent 6 months duration, as seen in the trials
All costs rounded to the nearest \$100

Limitations

- Lack of data on active comparator treatments
- Lack of long-run clinical evidence on discontinuation, benefits of pain reduction, and risks from using elagolix
- Available evidence from trials contributed to our need to calculate weighted average of response based on average menstrual cycle duration

Conclusions

- Findings suggest elagolix may provide marginal increases in quality-adjusted survival over no active medical management (placebo with non-specific rescue analgesics)
- With the evidence available at this time and the projected price, the estimated cost-effectiveness of elagolix 200 mg twice daily falls within the range of \$50,000 to \$150,000 per QALY gained

Public Comments Summary

- Elagolix for dysmenorrhea and nonmenstrual pelvic pain should be modeled together
- Societal perspective underestimates lost productivity
- Receipt of add-on treatment following surgery should be considered
- Maximum duration of elagolix should be considered

Supplemental Slides

Additional Key Assumptions

- Two time-horizons were estimated to reflect short-run (6mo) and long-run (18yr) use of elagolix.
- Women passing through the surgery state incurred a disutility from surgery.
- Women in post-hysterectomy health states incurred a disutility from the loss of fertility.
- Women responding and staying on elagolix were assumed to have a constant increased risk of CVD and FX (ages 40 – 50 only due to lack of evidence) compared to placebo.
- Transition probabilities for discontinuation due to lack of efficacy differ by treatment arm but not over time.

Parameters: Transition Probabilities

Input parameter	Value ^a	Lower	Upper
Pain recurrence (discontinuation due to lack of efficacy) risk ratio for elagolix vs. placebo	0.30	0.08	1.06
Proportion of women on elagolix treatment	0.981	0.83	1.0
Probability of subsequent surgery (conditional on prior surgery) ^b	0.0260	0.017	0.037
Probability of hysterectomy (conditional on prior surgery) ^b	0.0164	0.009	0.026
Probability of response to subsequent surgery ^b	0.4377	Not varied	
Probability of response to hysterectomy ^b	0.4970	Not varied	
Proportion who discontinued for pregnancy	0.0190	0	0.17
Probability of death from hysterectomy surgery ^b	0.0080	0.004	0.012

Parameters: Long-Run Adverse Events

Adverse Event	Elagolix 200 mg twice daily ^a	Placebo
Proportion of women with low bone mineral density on treatment (-1.5 z score or less)	0.041	0.002
Relative risk of fracture with a 1 SD decrease in bone mineral density (i.e., low bone mineral density)	1.5 (1.36, 1.65)	
Osteoporotic fracture risk for normal bone density (women aged 40-49) ^b	0.00065 (0.00063, 0.00067)	
Probability of cardiovascular disease ^{b,c}	0.00016	0.00015

Public Comment and Discussion

Casey Berna, MSW

Endometriosis and Infertility Patient Advocate

Conflicts of interest:

- None declared

Martin Robbins, MD

New England Center for Endometriosis

Conflicts of interest:

- None declared

Heather Guidone, BCPA

Patient Advocate; Program Director, Center for Endometriosis Care & Executive Board Member, Endometriosis Research Center

Conflicts of interest:

- None declared

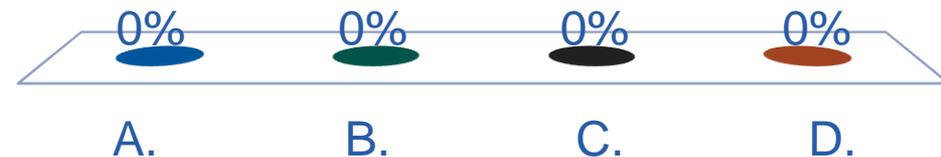
Voting Questions

WIFI Network: Student

Password: [Open Network]

0. What is the name of the folkloric sea monster that allegedly lives in Lake Champlain?

- A. Champ
- B. The Serpent
- C. Richard
- D. Dragonfish



Patient Population for all questions:
Adult premenopausal women with
symptomatic endometriosis and
moderate-to-severe symptoms.

1. Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by no treatment?

- A. Yes
- B. No



2. Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by the GnRH agonist, leuprorelin acetate?

A. Yes

B. No



3. Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by hormonal contraceptive, depot medroxyprogesterone?

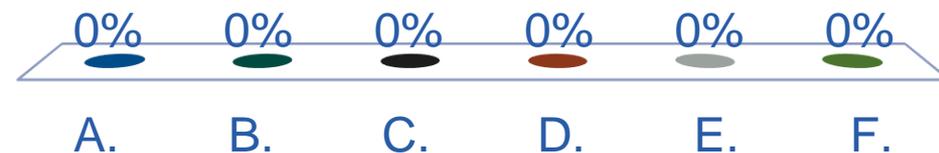
A. Yes

B. No



4. When compared to no treatment, does elagolix offer one or more of the following “potential other benefits”? (select all that apply)

- A. Reduced complexity
- B. Reduce important health disparities
- C. Reduce caregiver/family burden
- D. Novel mechanism of action or approach
- E. Significant impact on improving return to work/overall productivity
- F. Other important benefits or disadvantages.



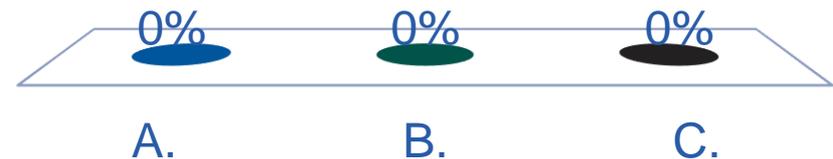
5. Are any of the following contextual considerations important in assessing long-term value for money? (select all that apply)

- A. Care for individuals with condition of high severity
- B. Care of individuals with condition with high lifetime burden of illness
- C. First to offer any improvement
- D. Compared to no treatment, there is significant uncertainty about long-term risk of serious side effects
- E. Compared to no treatment, there is significant uncertainty about the magnitude or durability of long-term benefits
- F. Other important contextual considerations.



6. Given the available evidence on comparative clinical effectiveness and the incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of elagolix compared with no active treatment?

- A. Low
- B. Intermediate
- C. High



Policy Roundtable

Endometriosis Policy Roundtable

Casey Berna, MSW

Endometriosis and Infertility Patient Advocate

Heather Guidone, BCPA

Patient Advocate; Program Director, Center for Endometriosis Care; Executive Board Member Endometriosis Research Center

William Brewster, MD, FACP, CHIE

Vice President
Harvard Pilgrim Health Care, New Hampshire Market

Nancy Hogue, PharmD

Director of Pharmacy Services
Department of Vermont Health Access

Rebecca Flyckt, MD

Director, Fertility Preservation Program, Obstetrics, Gynecology and Women's Health Institute
Cleveland Clinic

Elizabeth McGee, MD

Professor, Director of Reproductive Endocrinology and Fertility Division, Department of Obstetrics, Gynecology and Reproductive Services
University of Vermont Larner College of Medicine

Expert and CEPAC Panel Reflections

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on/about August 2
 - Includes description of CEPAC votes, deliberation; policy roundtable discussion
- Materials available at
<https://icer-review.org/topic/endometriosis/>

Adjourn