Elagolix for Endometriosis: Effectiveness and Value

Modeling Analysis Plan

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Institute for Clinical and Economic Review

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1. Approach

The primary aim of this analysis is to estimate the cost-effectiveness of elagolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, for the treatment of endometriosis-associated pain in adult, pre-menopausal women. Quality-adjusted survival and health care costs will be estimated for elagolix and relevant comparators using the health-care system perspective from the average age of treatment initiation of 32 years of age[1] until 50 years of age, within the average age of menopause onset.[2] Costs and outcomes will be discounted at 3% per year. Incremental costs and outcomes will be calculated comparing each intervention to its comparator. The model will be developed in Microsoft Excel. The model framework and assumptions are described in detail below.

2. Methods

2.1 Overview and Model Structure

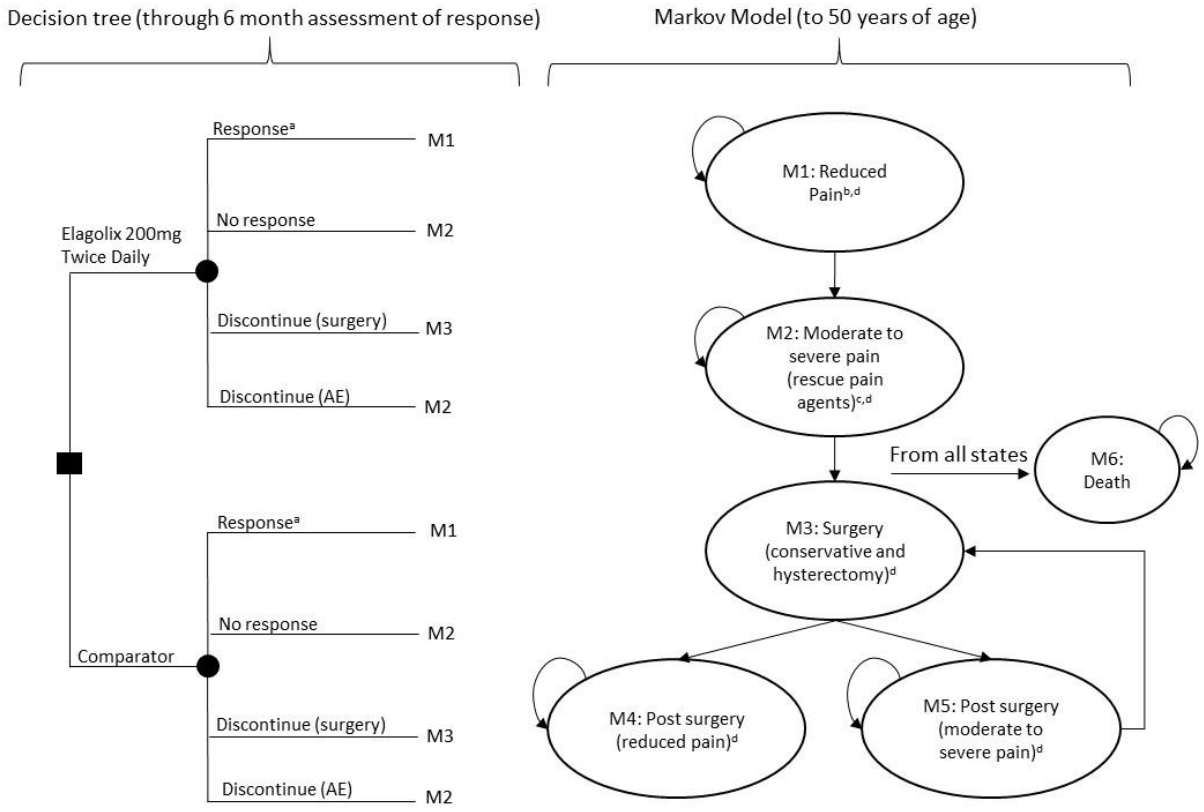
The decision analytic model structure will be informed by the primary aim, previous modeling evidence, Phase III clinical trials for elagolix, and stakeholder input. The model will include a short-term decision tree and a long-term Markov model to evaluate the cost-effectiveness of elagolix compared to relevant comparators for the management of pain associated with endometriosis. Consistent with the pivotal clinical trial duration, the decision tree will calculate the costs and consequences of six months of treatment with elagolix, including pathways relevant to short-term outcomes, such as response to treatment (e.g. pain reduction).[3] Long-term outcomes, such as pain recurrence and surgery,[4] will be assessed via a Markov model. In the long-term Markov model, patients will transition between endometriosis pain-related health states during three-month cycles over the model time horizon. The model time horizon is approximately 18 years, ending at 50 years of age, within the average age of menopause onset (Figure 1).[2] Serious adverse clinical events were rarely observed within the randomized controlled trials and therefore will not be emphasized within the decision-tree. Long-term elagolix and comparator exposure, and the corresponding associations with adverse events such as fracture risk and cardiovascular disease, will be included in the model using best available evidence on the rate of women developing such events.

Each intervention will be evaluated in terms of the proportion with clinical response (with respect to reduction in dysmenorrhea-related and non-menstrual pelvic pain) at six months using a decision tree. The decision tree will be used to inform two versions of the same Markov model; both versions assessing long-run costs and outcomes of treatment with elagolix and comparators for dysmenorrhea-related pain, and separately, non-menstrual pelvic pain. Response to dysmenorrhea-related pain and non-menstrual pelvic pain in the decision tree will determine the initial state distribution of patients on elagolix and comparators in the long-run Markov model. This modeling framework will be used for two reasons: 1) response to dysmenorrhea-related pain and non-

menstrual pelvic pain was not presented in aggregate form; and 2) the numeric pain rating scale was not reported by dysmenorrhea-related pain and non-menstrual pelvic pain, therefore mapping to a utility score by specific pain symptom will not be possible.

Women that respond to treatment will move to the reduced pain (M1) Markov model state and will continue on current therapy until discontinuation from lack of efficacy. In the elagolix arm, a constant proportion of women will not incur costs of elagolix to allow for attempted and successful pregnancies based on rates of pregnancies observed in the trial. Those that do not respond by six months will move to the moderate to severe pain (M2) Markov model state where they will be treated with rescue analgesics (e.g., NSAID, opioid). A small proportion of non-responders will discontinue treatment with rescue analgesics and move directly to the surgery (M3) Markov health state at the end of six months. Women may continue in the moderate to severe pain state (M2) until opting for surgery. After surgery, the model is flexible to allow for a proportion to respond with reduced pain (M4) and the remaining proportion to not respond to surgery (M5). A repeat and final surgery (i.e., hysterectomy) may occur, where again, women may respond with reduced pain or not respond with continued moderate to severe pain. Women in M1 and M4 will incur costs for analgesics at half the cost (assumed) of those in the M2, M3, and M5 states. This assumption supports the clinical trial evidence that pain management utilization is likely higher and perhaps twice as high in the moderate to severe pain state as compared to the reduced pain state with or without elagolix add-on treatment. Death can occur from any state in the model.

Figure 1. Model Framework



Abbreviations: AE = adverse event
a. Women with pain reduction and decreased or stable use of rescue analgesics stratified by dysmenorrhea and non-menstrual pelvic pain and aggregated across elagolix trials, EM-I and EM-II
b. Women in M1 continue on Elagolix or active comparator until recurrence of pain (discontinuation due to lack of efficacy) and movement to M2; a constant proportion of women will not incur costs of elagolix to allow for attempted and successful pregnancies based on rates of pregnancies observed in the trial.
c. M3 is a surgery tunnel state incurring the costs of surgery and the disutility from surgery and moderate to severe pain. Surgeries may occur after the 6-month duration of the trial; from the moderate to severe pain state (e.g., laparoscopy, excision/ablation/fulguration, etc.); and a final repeat surgery (assumed hysterectomy)
d. All states include the cost for treating a proportion of women on NSAID and opioid therapy for pain management.

Key model inputs will include clinical response and recurrence rates, quality of life values, occurrence of long-term adverse events, costs of drug treatment, surgery, other endometriosis-related health care services, and mortality. Probabilities, costs, and other inputs will differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions.

Outcomes from the decision tree and Markov model will include total treatment and non-treatment costs, long-term adverse event costs, quality-adjusted life years (QALYs), and incremental cost per QALY gained.

2.2 Target Populations

The population of focus for this review is adult premenopausal women with symptomatic endometriosis. Characteristics of the modeled population are aggregated (i.e., as weighted averages) from the elagolix clinical trials and are shown in Table 1.

Table 1. Base-Case Model Cohort Characteristics (aggregate of EM-I and EM-II for placebo and Elagolix 200mg Twice Daily)[1]

Cohort Characteristic	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 non-menstrual pain [0 (none) – 3 (severe)]	1.6 ± 0.5
Score on numeric rating scale [0 (none) – 10 (worst)]	5.5 ± 1.7

2.3 Treatments

Interventions

The list of interventions was developed with input from patient organizations, clinicians, manufacturers, and payers on which treatments to include. The full list of interventions is as follows:

- Intervention: Elagolix 200mg Twice Daily

Comparators

Comparator selection was developed with input from stakeholders. The comparators are detailed below.

- Primary comparator: Comparator 1: Placebo (primary comparator)
- Secondary comparators: GnRH agonist, Hormonal contraceptives, Aromatase inhibitors

The primary comparator is consistent with the randomized controlled trial evidence. Secondary comparators will be modeled provided sufficient and consistent evidence is available from the clinical review.

2.4 Key Model Choices and Assumptions

The base case analysis will take a health system perspective and thus focus on direct medical care costs only. Outcomes will be estimated until 50 years of age, the average age of menopause onset, to capture the potential lifetime impacts of short-term and ongoing treatment with elagolix and

pain management. Costs and outcomes will be discounted at 3% per year. Model assumptions are described in Table 2.

Table 2. Key Model Assumptions

Assumption	Rationale
Patients not responding to treatment after the first six months will not be re-treated on elagolix and move directly to treatment with pain agents and/or surgical procedures.	Re-treatment with elagolix was not attempted for women who did not respond in clinical trials. The re-treatment efficacy of elagolix is unknown.
Endometriosis-related treatment has no direct effect on mortality.	There is no direct evidence linking treatment to decreased mortality.
The proportion of patients responding to treatment will continue on treatment until discontinuation due to lack of efficacy with recurrence to moderate to severe pain immediately following discontinuation.	Women responding to treatment stay on treatment to avoid recurrence of pain symptoms.
Transition probabilities for discontinuation due to lack of efficacy differ by treatment arm (i.e., elagolix and comparator) but do not vary over time.	There is no available evidence on time-varying discontinuation rates for elagolix.
A constant proportion of women on elagolix each cycle is assumed to be off treatment for attempted and successful pregnancies.	Trial evidence shows women discontinued to attempt pregnancy, but there was no evidence suggesting they would permanently discontinue treatment post-delivery.
Women passing through the surgery state incur a disutility from surgery in addition to the disutility of moderate to severe pain during the surgery time cycle.	Evidence suggests there is a temporary quality of life decrement related to surgery above and beyond moderate to severe pain.
Women in post-hysterectomy health states incur a disutility from the loss of fertility.	Evidence suggests there is a decrement to quality of life related to the loss of fertility.
Women responding and staying on elagolix are assumed to have an increased risk for cardiovascular disease and fracture risk as compared to placebo.	Trial evidence suggests changes in lipid panels and bone mineral density that may increase the risk of cardiovascular disease and fractures as compared to age-matched peers not on elagolix.
All states include the cost for treating a proportion of women on NSAID and opioid therapy for pain management. The cost incurred in the pain reduced states is assumed half of the cost of NSAID and opioid therapy use in moderate to severe pain health states.	Trial evidence indicated a reduction in the use of rescue pain agents by women responding to elagolix, not complete discontinuation.

2.5 Input Parameters

Model inputs were estimated from the clinical review, as well as from published literature and information provided by stakeholders. The inputs that informed the model are described below.

Clinical Inputs

Treatment Response

Treatment response rates were obtained from published literature and information provided from manufacturer. Initial response rates used in the short-term decision tree are provided in Table 3.

Table 3. Treatment Response Rates (aggregate of EM-I and EM-II trials through 6 months)[1]

	Elagolix 200mg Twice Daily*	Comparator (Placebo)*
Response at 6 months [dysmenorrhea]	76.1%	24.2%
Response at 6 months [non-menstrual pelvic pain]	62.1%	37.7%
Proportion who discontinued due to adverse events	5.5%	6.0%
Proportion who discontinued due to surgery	0.6%	1.4%

*95% confidence intervals will be included in sensitivity analyses

Inputs to inform the transition probabilities between the Markov model health states are detailed in Table 4. These probabilities were obtained from published literature and information provided from the manufacturer.

Table 4. Transition Probabilities for Markov model

Input parameter	Value[a]	Source
Probability of pain recurrence (discontinue due to lack of efficacy): Elagolix 200mg Twice Daily (responders)[b]	0.0031	Taylor, 2017[1]
Probability of pain recurrence (discontinue due to lack of efficacy): Placebo (responders)[b]	0.0104	Taylor, 2017[1]
Probability of subsequent surgery (conditional on prior surgery)[b]	0.0260	Soliman, 2016[5]
Probability of hysterectomy (conditional on prior surgery) [b]	0.0164	Soliman, 2016[5]
Probability of response to subsequent surgery[b]	0.4377	Soliman, 2016[5]
Probability of response to hysterectomy[b]	0.4970	Soliman, 2016[5]
Proportion who discontinued for pregnancy	0.0190	Taylor, 2017[1]
Probability of death from hysterectomy surgery[b]	0.0080	Makinen, 2001[6]

[a] Input parameters will be varied in sensitivity analyses; [b] 3-month cycle length probabilities

Adverse Events

Given the trial for elagolix did not reveal any serious grade 3/4 adverse events, the model will focus on estimating the impact of changes in clinical markers from elagolix and comparator treatment on long-run adverse events. Long-run adverse event model parameters are shown in Table 5. Specifically, fracture risk and cardiovascular disease are both modeled beginning at 40 and 32 years of age, respectively.[7,8] The model applies a cost to treat fractures and a disutility to the proportion of women with low bone mineral density from elagolix and comparators. Those on elagolix have an increased risk of fractures based on low bone mineral density. The model separately applies a cost and disutility to manage cardiovascular disease for elagolix and comparators. The model does not apply an increased risk of mortality from fractures or cardiovascular disease.

Table 5. Risks of long-term adverse events included in model

Adverse Event	Elagolix 200mg Twice Daily[a]	Placebo	Source
Proportion of women with low bone mineral density on treatment (-1.5 z score or less)	0.041	0.002	Taylor, 2017[1]
Relative risk of fracture with a 1 SD decrease in bone mineral density (i.e., low bone mineral density)	1.5		Kanis, 2001[8]
10-Year osteoporotic fracture risk for normal bone density (women aged 40-49)[b]	0.00065		Looker, 2017[9]
Probability of cardiovascular disease[b,c]	0.00016	0.00015	D'Agostino, 2008[7]

[a] Risk inputs will be varied in sensitivity analyses
[b] 3 month cycle length probabilities
[c] Risk calculation based on average lipid panels at end of trial for each group

Utility Inputs

Model Health States

To adjust for quality of life, utilities will be applied for each model health state. Health state utilities will be derived from publicly available literature and applied to the disease states. Utilities may differ by population but will remain consistent within a population across different treatments. The utilities for each model health state are presented in Table 6. To calculate the mean utility for the moderate to severe pain health state, we rely on a mapping function between the numerical pain rating scale and the EQ-5D.[10] Baseline numerical pain rating scores were consistent across treatment arms in EM-I and EM-II, and therefore serve as a baseline pain level for the modeled population.[1] Disutilities from surgical procedures are applied to those experiencing moderate to severe pain only during the tunnel cycle when the surgery occurs. A disutility related to the loss of fertility is applied to both subsequent health states post-hysterectomy.

Table 6. Model Health State Utilities

Health State	Utility	Source
Mean EQ-5D health utility for women in the United States without pain	0.92	Sullivan, 2006[11]
Moderate to severe pain health state	0.73	Dixon, 2011[10]
Surgical disutility (e.g., laparoscopy)	-0.06	Ganz, 2013[12]
Surgical disutility (hysterectomy)	-0.07	Ganz, 2013[12]
Loss of fertility disutility (all subsequent hysterectomy health states)	-0.07	Ganz, 2013[12]

[a] Utility inputs will be varied in sensitivity analyses

Treatment Disutilities

Disutilities will also be applied for the proportion of women developing long-run adverse events. Table 7 details the disutilities applied for each adverse event. The utility of cardiovascular disease is subtracted from the overall utility of the proportion with cardiovascular disease within each health state. The disutility of a fracture is applied for the duration of the cycle length only for those experiencing a fracture event.

Table 7. Adverse Event-Related Disutilities

Health State	Utility/Disutility	Notes	Source
Cardiovascular disease	0.716		Sullivan, 2006[11]
Fracture	-0.04		Peasgood, 2009[13]

Cost Inputs

Drug Acquisition Costs

The unit cost for each treatment is reported in Table 8. We will use the Federal supply schedule (FSS) prices for comparator drugs since we did not find a robust estimate of net price from the SSR Health database. Discounts and rebates will not be assumed for generic drugs. For interventions without a list price, we will assume the price provided by the manufacturer. If neither a manufacturer-provided nor list price is available, threshold prices will be calculated at the three cost-effectiveness thresholds ($50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained).

Table 8. Drug Cost Inputs

Treatment and dose	Unit	WAC per Unit*	Net price per unit+
Elagolix 200mg x 2 threshold price	1	Threshold price to be estimated	Threshold price to be estimated
GnRH agonist Lupron Depot (Leuprolide Acetate 11.25mg	1	$3,673.40	$1,188.31
Naproxen sodium (550mg once daily)	1	$2.58	$2.58
Hydrocodone in Acetaminophen (10mg Hydrocodone/325mg Acetaminophen)	1	$0.90	$0.90

*WAC as on February 25th, 2018
+FSS price as on February 2nd, 2018

Healthcare Utilization Inputs

Additional healthcare utilization could occur with treatment monitoring and post-treatment. Table 9 details the healthcare utilization rates used for the long-run Markov model.

Table 9. Mean Rate of Healthcare Utilization per Patient Receiving Treatment

Category	Reduced Pain	Moderate to Severe Pain	Source
Outpatient visits per year	9	13	Fuldeore, 2015[14]

Health Care Utilization Costs

Costs associated with healthcare utilization that result from surgical procedures and long-run adverse events from treatment of endometriosis will be included in the model. Table 10 details the healthcare utilization unit costs that will be used in the model. Unit costs for healthcare utilization were the same across different treatments and populations.

Table 10. Unit Costs for Healthcare Utilization

Input	Value	Source
Laparoscopic surgery (per event)	$5,433	Fuldeore, 2011[15]
Hysterectomy (per event)	$14,437	Fuldeore, 2011[15]
Outpatient visits	$74.16	Physician fee schedule[16]

*Inflated to 2017 US dollars. They will be inflated to 2018 US dollars when an inflation index is available for 2018. All other costs reflect 2017 US dollars.

Adverse Event Costs

Long-run adverse event costs will be applied to patients with risk of long-run adverse events. Unit costs for each adverse event are stated in Table 11.

Table 11. Adverse Event Unit Costs

Long-Run Adverse Event (ICD-9-CM)	Mean ($)	Source
Fracture treatment cost (per event)	$7,093	Blume, 2011[17]
Cardiovascular disease management (per cycle)	$1,170	Mahoney, 2008[18]

All costs inflated to 2017 US dollars. They will be inflated to 2018 US dollars when an inflation index is available for 2018.

2.6 Model Outcomes

The model will estimate treatment response as well as the total health care costs to treat each patient by pain symptom (dysmenorrhea and non-menstrual pelvic pain). Unadjusted and utility-adjusted time spent in each health state will be summed across model cycles to provide estimates of life expectancy and quality-adjusted life expectancy.

Model outcomes of interest will include:

- By intervention with results split by dysmenorrhea-related pain and non-menstrual pelvic pain:
    - Within-trial and long-run quality adjusted life years (undiscounted and discounted)
- Pairwise comparisons:
    - Within-trial and long-run incremental cost-effectiveness ratios (per quality-adjusted life year gained) for each intervention versus the comparator

2.7 Analysis

Each model cycle will last three months. Patient quality-adjusted survival and health care costs will be estimated for each model cycle and then summarized over the model time horizon for each treatment option. Differences in quality-adjusted survival and costs between each treatment and comparator will be used to calculate incremental cost-effectiveness ratios.

Sensitivity Analysis

We will conduct one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic sensitivity analyses will also be

performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Additionally, we will perform a threshold analysis by systematically altering the price of the acquisition cost for each treatment option to estimate the maximum prices that would correspond to given willingness to pay (WTP) thresholds.

Scenario Analyses

Given available evidence on patient health-state level costs and lost productivity to the patient and caregiver, the perspective will be expanded to a modified societal one. Additional scenario analyses may include time-varying discontinuation rates/probabilities by cycle given evidence availability.

Model Validation

We will use several approaches to validate the model. First, we will provide preliminary methods and results to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we will refine data inputs used in the model, as needed. Second, we will vary model input parameters to evaluate face validity of changes in results. We will perform model verification for model calculations using reviewers. Finally, we will compare results to other cost-effectiveness models in this therapy area.

2.8 Acknowledgements

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