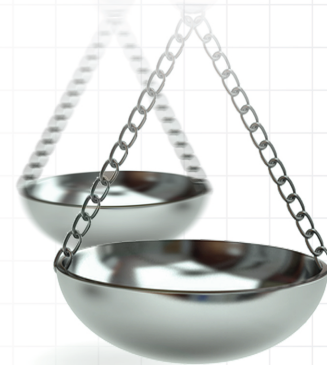




Cost-effectiveness of elagolix versus leuprolide acetate for treating moderate-to-severe endometriosis pain in the USA

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Aim: To assess the cost-effectiveness of elagolix versus leuprolide acetate in women with moderate to severe endometriosis pain. **Methods:** A Markov model was developed. The efficacy of leuprolide acetate was derived from statistical prediction models using elagolix trial data. Model inputs were extracted from Phase III clinical trials and published literature. **Results:** Compared with leuprolide acetate, elagolix generated positive net monetary benefit (NMB) assuming a payer's willingness-to-pay threshold of US\$100,000 per quality-adjusted life year over a 1-year time horizon: US\$5660 for elagolix 150 mg and US\$6443 for elagolix 200 mg. The 2-year NMBs were also positive. **Conclusion:** Elagolix was cost-effective versus leuprolide acetate in the management of moderate to severe endometriosis pain over 1- and 2-year time horizons. Results were robust in sensitivity analyses.

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Endometriosis is a chronic gynecological condition defined by the presence of endometrial glands and stroma outside the uterus [1]. The estimated prevalence of endometriosis ranges between 4 and 10% among women in their reproductive years [2–4]. Endometriosis manifests with pain symptoms – including nonmenstrual pelvic pain (NMPP), dysmenorrhea (DYS; painful menstruation) and dyspareunia (painful intercourse) [5] – that are often severe enough to result in decrements in quality-of-life and productivity in the workplace and at home [6–8]. Due to the nonspecific nature of pain, patients are often diagnosed about 7 years after symptom onset, at which time they typically would have accrued a substantial burden of disease [9–12]. A retrospective analysis of women with endometriosis using a commercial database between 2010 and 2014 found that they incurred US\$10,002 and US\$2132 in direct and indirect healthcare costs per year, respectively, more than matched women without endometriosis [13]. Efforts are ongoing to improve the awareness and diagnosis of endometriosis, including the standardization of transvaginal ultrasonography terminologies by the International Deep Endometriosis Analysis (IDEA) group [14].

Pain management is the cornerstone of endometriosis treatment and for patients with moderate to severe pain, it often involves repeated courses of medical therapy, surgery or both [15]. In the absence of contraindications, nonsteroidal anti-inflammatory drugs, cyclical combined oral contraceptives and progestins are common first-line medical therapies for endometriosis [15,16]. If pain persists, a switch to continuous combined oral contraceptives or a levonorgestrel intrauterine system may be warranted. If these approaches are not effective, gonadotropin-releasing hormone (GnRH) agonist therapy, for example, with leuprolide acetate [17], can be appropriate per clinical guidelines [5,15]. However, while GnRH agonist therapy is effective in controlling pain, it also has considerable side effects due to the induced hypoestrogenic state. This may lead to bone loss of up to 13% over a period of

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6 months, requiring progestogen add-back therapy from 6 months to a maximum of 1-year treatment as per US FDA approval [17,18]. Surgical approaches – including laparoscopy, hysterectomy and laparotomy – can be used as first-line therapy or after failed medical therapies [5,15,19]. However, in addition to its invasiveness, surgery often does not resolve endometriosis pain and is associated with recurrence of pain requiring additional therapy (in 30–60% of patients) within 6 to 12 months post-surgery [15]. There is thus an unmet need for more effective, better tolerated and safer treatment for moderate to severe endometriosis pain.

In July 2018, the FDA approved elagolix (ORILISSA™), an oral GnRH antagonist specifically developed for women with moderate to severe pain associated with endometriosis [20,21]. Patients initiate treatment with elagolix 150 mg once daily (QD) for a maximum of 24 months or 200 mg twice daily (BID) for a maximum of 6 months [21]. The FDA approval of elagolix was based on data from two multinational, double-blind, placebo-controlled Phase III trials – Elaris Endometriosis I and II (EM-I and EM-II) [22] – involving almost 1700 premenopausal women with moderate to severe pain associated with endometriosis; the coprimary end points were the proportion of patients whose DYS or NMPP responded to treatment at month 3. The trials revealed that, compared with placebo, patients treated with elagolix 150 mg QD and 200 mg BID had significantly reduced DYS and NMPP pain. The 200 mg BID dosage also led to a significant reduction of dyspareunia. Most common adverse reactions (>5%) in trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions and mood changes [21,22].

Elagolix has not yet been assessed for its cost-effectiveness relative to current medical treatments for moderate to severe endometriosis pain. Although the Institute for Clinical and Economic Review (ICER) recently completed a review of elagolix for moderate to severe endometriosis pain, it was relative to placebo or no active treatment [23]. The objective of the present study was to estimate the cost-effectiveness of elagolix relative to the GnRH agonist leuprolide acetate, the most commonly used second-line medical treatment for endometriosis according to an internal analysis of Truven health insurance claims in 2016 (see Supplementary Material B). The analysis was conducted from the perspective of a US managed care organization that only considered direct medical care costs. Specifically, a cost-effectiveness model (CEM) was developed to assess the 1- and 2-year cost-effectiveness of 24-month treatment with elagolix 150 mg QD and 6-month treatment with elagolix 200 mg BID, each relative to 12-month treatment with leuprolide acetate plus 6-month add-back therapy, in a hypothetical population of women with moderate to severe endometriosis pain. The duration of each treatment was determined by the treatment's label [17,21].

Methods

A summary table of model assumptions is presented in Supplementary Material A.

Model structure

Developed as a health-state (Markov) transition model, the CEM included twelve (12) health states: three on-treatment symptom severity states (no/mild symptoms; moderate symptoms; severe symptoms), two off-treatment symptom severity states (off-treatment with no/mild symptoms; other medical treatment with moderate/severe symptoms), six surgery and post-surgery states (first laparoscopy; post-first laparoscopy; second laparoscopy; post-second laparoscopy; hysterectomy; post-hysterectomy) and one absorbing mortality state. Permissible transitions between these health states, depicted as arrows in Figure 1, were assumed to take place at the beginning of each 3-month Markov cycle.

Patients entered the CEM through its three on-treatment symptom severity states for two endometriosis symptoms: DYS and NMPP. The severity of each symptom was defined by the Endometriosis Daily Pain Impact Diary (EDPID) score: 0/1 = no/mild, 2 = moderate and 3 = severe [24]. From their initial state, patients transitioned from a worse severity state to a better severity state per treatment-specific symptom response rates. To combine the two symptoms, equal weights were assigned to each symptom (varied in sensitivity analysis from 0 to 100% DYS). The resulting weighted averages were used for all symptom-related model inputs.

Two off-treatment states captured treatment discontinuation (unplanned) or completion (planned) with elagolix or leuprolide acetate. Upon treatment discontinuation or completion, patients with no/mild symptoms transitioned to 'off-treatment with no/mild symptoms' while patients with moderate/severe symptoms transitioned to 'other medical treatment with moderate/severe symptoms'. For cycles before the treatment-specific model duration of treatment (DOT), treatment-specific premature discontinuation rates were estimated from the treatments' Phase III trials. All remaining patients transitioned to their respective off-treatment state upon reaching the treatment-specific

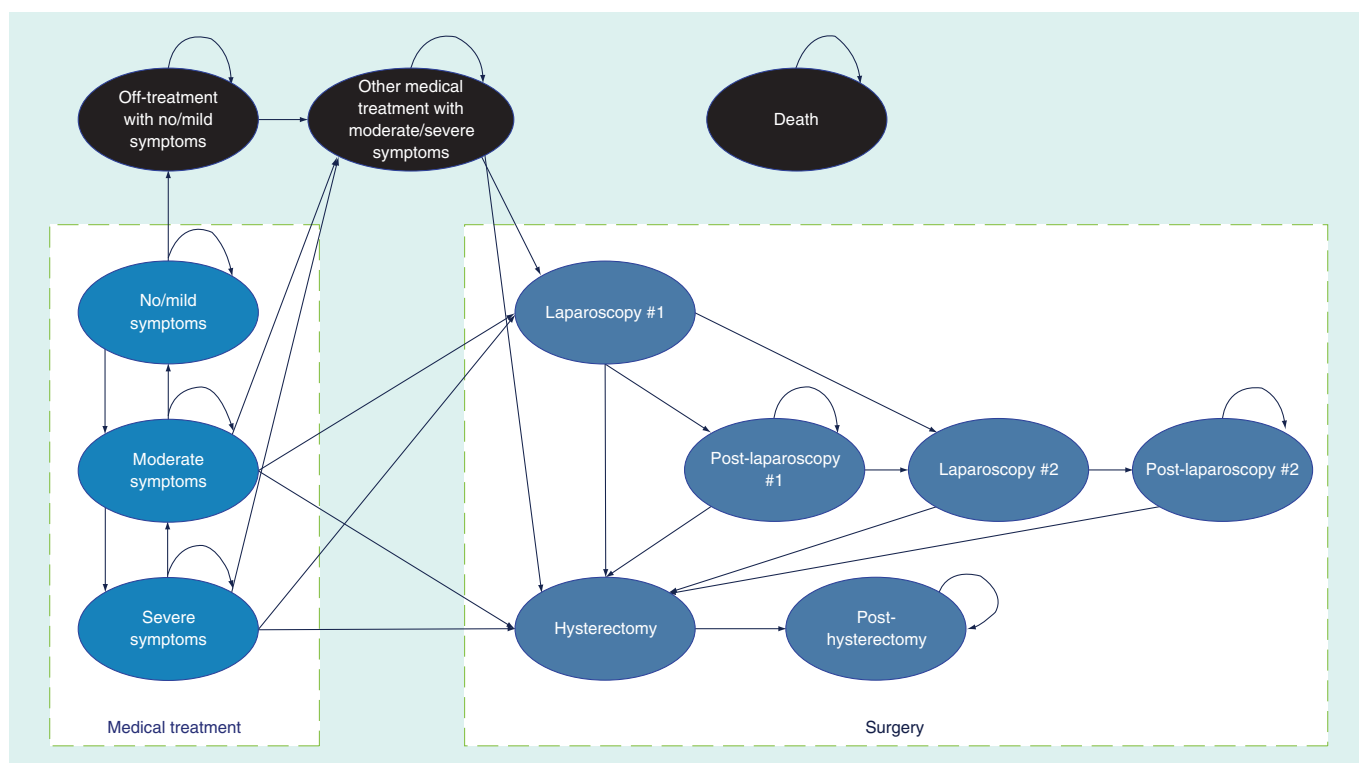


Figure 1. Cost-effectiveness model structure. Health states are depicted by ellipses, while arrows represent permissible transitions between health states. Transition to all-cause death is possible from all states. Transition to operative death is possible from states: 'laparoscopy #1', 'laparoscopy #2' and 'hysterectomy'.

model DOT. Patients in the 'off-treatment with no/mild symptoms' state could experience symptom recurrence and transition to 'other medical treatment with moderate/severe symptoms'. Patients in states with moderate/severe symptoms could receive up to two laparoscopies; those not wanting to preserve their fertility could also receive hysterectomy. A proportion of patients in the post-surgery states were assumed to still experience symptoms and therefore, received other medical treatments. Finally, patients could transition to all-cause death from any state based on the natural death rate; patients undergoing surgery faced additional risk of operative death.

The model was constructed in Microsoft Excel 2016 (Microsoft Corporation, WA, USA).

Study population

The study population comprised 1686 patients enrolled in the Phase III trials of elagolix, namely, premenopausal women between the ages of 18 and 49 years who had received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate or severe endometriosis-associated pain. It was assumed that patients were evenly distributed between moderate and severe pain, faced an all-cause death rate associated with a baseline age of 32 years and were all eligible to receive hysterectomy. Baseline patient characteristics in the model are summarized in Table 1.

Intervention & comparator

The model comparator was 12-month treatment with leuprolide acetate plus 6-month add-back with norethindrone acetate (NA) in the latter half of treatment. Leuprolide acetate was administered as an intramuscular injection of 11.25 mg every 3 months for a maximum of four injections. Add-back was administered as 5 mg NA tablets per day for 6 months [17]. For the intervention, both FDA-approved regimens of elagolix were assessed relative to the comparator.

Table 1. Baseline patient characteristics in the model.

Characteristic	Base	Low	High	DSA Info: low and high source	PSA info: SE used; assumed distribution	Source/note
Symptom severity distribution:						
– Moderate	50.0%	40.0%	60.0%	Assumed	Calculated [†] ; β	Assumed
– Severe	50.0%	60.0%	40.0%	Assumed	100% – moderate	Assumed
Age (years)	32			Not varied	Not varied	Weighted average age across all patients in Elaris EM-I and EM-II [22]
Proportion preserving fertility	0.0%	0.0%	10.0%	Assumed	Calculated after adding 1% [†] ; β	Assumed; patients preserving fertility were not eligible to receive hysterectomy
Proportion of DYS vs NMPP in combined inputs	50.0%	0.0%	100.0%	$\pm 20\%$	Calculated [†] ; β	Assumed

[†]SE calculated as $([\text{base-low}] + [\text{high-base}]) / (2 \times 1.96)$.
 DSA: Deterministic sensitivity analysis; DYS: Dysmenorrhea; NMPP: Nonmenstrual pelvic pain; PSA: Probabilistic sensitivity analysis; SE: Standard error.

Model inputs

Treatment efficacy

The efficacy of elagolix and leuprolide acetate at eliciting clinical response with respect to moderate to severe DYS and NMPP was each assessed in Phase III trials: elagolix in EM-I and EM-II [22] and leuprolide acetate in Schlaff *et al.* [25] and Crosignani *et al.* [26]. However, the treatments' trials used different definitions for response: elagolix's trials used response rates calculated from self-administered daily EDPID scores and a receiver operating characteristics (ROC)-determined threshold [22] while leuprolide acetate's trials used response rates calculated from clinician-administered monthly Biberoglu and Behrman (B&B) scores and a 1-point threshold [27]. Although the B&B scale is the most commonly used instrument for assessing endometriosis symptoms in a clinical setting, compared with EDPID scores, there is potential recall bias (monthly vs daily reference point) and rater bias (including inter- and intra-rater variability) arising from being clinician- versus self-administered [28].

To reconcile the differences in DYS and NMPP response measurement methodologies, patient-level data from EM-I and EM-II were used to develop statistical prediction models that mapped patient characteristics to 6-month DYS and NMPP response probabilities calculated from daily EDPID scores and the ROC-determined threshold. Predictions of DYS and NMPP response for leuprolide acetate were then generated as the cross-product of the mean predictor values from the leuprolide acetate trials [25,26] and their corresponding fitted coefficients. The technical details of this prediction are described in Supplementary Material D. All model inputs related to treatment efficacy are described in Table 2.

Natural history transition probabilities

Transition probabilities not specific to treatment were either obtained from published literature or assumed, including probabilities for symptom recurrence, surgery and death. Calculated 3-month transition probabilities (or proportions) that did not differ by treatment are summarized in Table 3 [29].

For patients who did not discontinue treatment, experience symptom response or undergo surgery, a small proportion (2.5%) was assumed to transition from a better on-treatment symptom severity state to a worse one, while the rest (97.5%) remained in their current state. After treatment discontinuation, the probability of symptom recurrence was derived from a study on the cumulative recurrence rates of pain after depot medroxyprogesterone acetate (DMPA) treatment, which was 18% at 12 months [30].

Probabilities of initial surgery (laparoscopy or hysterectomy) were derived from a retrospective claims analysis of the usage of surgical procedures following leuprolide acetate initiation among women with endometriosis. In their first year after leuprolide acetate initiation, 4.2% (11.7%) of women underwent laparoscopy (hysterectomy) [31]. After the first laparoscopy, probabilities for another laparoscopy or hysterectomy were derived from another claims database analysis on retreatment rates among endometriosis patients with laparoscopy: 3.2% (5.6%) experienced another laparoscopy (hysterectomy) within 1 year of their index laparoscopy [32]. In the post-surgery states, the

Table 2. Treatment efficacy in the model.

3-month transition probabilities	Base	Low	High	DSA info: low and high source	PSA info: SE used; assumed distribution	Source/note
Elagolix 150 mg QD:						
– Premature discontinuation	11.3%	9.0%	13.5%	±20%	Calculated [†] ; β	Taylor <i>et al.</i> [22]
– DYS response	22.2%	17.8%	26.6%	±20%	Calculated [†] ; β	Phase III elagolix data for treatment completers (see Supplementary Material D)
– NMPP response	26.2%	21.0%	31.5%	±20%	Calculated [†] ; β	Phase III elagolix data for treatment completers (see Supplementary Material D)
Elagolix 200 mg BID:						
– Premature discontinuation	12.3%	9.8%	14.7%	±20%	Calculated [†] ; β	Taylor <i>et al.</i> [22]
– DYS response	41.5%	33.2%	49.8%	±20%	Calculated [†] ; β	Phase III elagolix data for treatment completers (see Supplementary Material D)
– NMPP response	33.1%	26.5%	39.7%	±20%	Calculated [†] ; β	Phase III elagolix data for treatment completers (see Supplementary Material D)
Leuprolide acetate (±NA):						
– Premature discontinuation	8.5%	6.8%	10.1%	±20%	Calculated [†] ; β	Schlaff <i>et al.</i> [25]; Crosignani <i>et al.</i> [26]
– DYS response	38.5%	30.8%	46.2%	±20%	Calculated [†] ; β	Phase III elagolix data for treatment completers (see Supplementary Material D); Schlaff <i>et al.</i> [25]; Crosignani <i>et al.</i> [26]
– NMPP response	36.1%	28.9%	43.3%	±20%	Calculated [†] ; β	Phase III elagolix data for treatment completers (see Supplementary Material D); Schlaff <i>et al.</i> [25]; Crosignani <i>et al.</i> [26]

[†] SE calculated as $(\text{[base-low]} + \text{[high-base]}) / (2 \times 1.96)$.

BID: Twice a day; DOT: Duration of treatment; DSA: Deterministic sensitivity analysis; DYS: Dysmenorrhea; NA: Norethindrone acetate; NMPP: Nonmenstrual pelvic pain; PSA: Probabilistic sensitivity analysis; QD: Once a day; SE: Standard error.

proportions of patients experiencing moderate to severe pain and receiving other medical treatments were derived from a claims data analysis that found 19.6% (1.9%) of the patients with laparoscopy (hysterectomy) received second-line therapy (i.e., GnRH agonists, progestin and danazol) by 3 months [33].

The rate of operative death due to laparoscopy was 3.33 per 100,000 [34], while the rate of operative death due to hysterectomy was 38 per 100,000 [35]. Annual probabilities of background death for females were obtained from US life tables for 2014 [36].

Adverse events

In the model, only patients in on-treatment states were at risk of experiencing treatment-related adverse events (AEs), including breast pain, depression, headache, hot flushes, libido decrease, nausea and weight gain. It was assumed that AEs negatively impact health state costs (increase) and utilities (decrease). Treatment-related AE rates of any severity were obtained from the AE occurrence data collected in EM-I and EM-II [37] and leuprolide acetate's prescribing information [17]. Weighted average 6-month AE rates were adjusted to 3-month rates and presented in Table 4. The AE rates for 'other medical treatments' were assumed to be the averages of all treatments' rates.

Patients in surgical states were at risk of surgery-related complications. Rates of surgery-related complications were obtained from the 3-month results of a published retrospective claims analysis of endometriosis patients, where 13.7% (25.1%) of endometriosis patients with laparoscopy (hysterectomy) developed complications within 3 months of surgery (36.4% [46.0%] within 12 months of surgery as published) [33].

Of note, although bone mineral density (BMD) loss is a known AE of medical endometriosis treatments, modeling BMD loss in terms of fracture risk was excluded given its expected negligible impact on model results. Specifically, the fracture risk estimated by the FRAX score (US Caucasian) for a woman who might have been in EM-I or EM-II was only 0.1% over 10 years (0.01% over 1 year) [38,39] (we estimated the 10-year risk of hip fracture risk for a representative woman included in the EM-I and EM-II trials assuming: body mass index [BMI] = 27, no previous fractures, no parent fractured hip, no current smoking, no glucocorticoids, no rheumatoid arthritis, no

Table 3. Natural history transition probabilities in the model.

3-month transition probabilities (unless specified otherwise)	Base	Low	High	DSA info: low and high source	PSA info: SE used; assumed distribution	Source/note
Symptom recurrence:						
– On-treatment: proportion that worsen (vs remain the same)	2.50%	2.00%	3.00%	±20%	Calculated [†] ; β	Assumed
– Off-treatment: from ‘off-treatment with no/mild symptoms’ to ‘other medical treatment with moderate/severe symptoms’	4.84%	3.87%	5.81%	±20%	Calculated [†] ; β	Cheewadhanaraks [30] [‡]
Surgery with moderate/severe symptoms:						
– To ‘laparoscopy #1’ from: ‘moderate symptoms’; ‘severe symptoms’; or ‘other medical treatment with moderate/severe symptoms’	1.08%	0.86%	1.29%	±20%	Calculated [†] ; β	Soliman <i>et al.</i> [31] [§]
– To ‘hysterectomy’ from: ‘moderate symptoms’; ‘severe symptoms’; or ‘other medical treatment with moderate/severe symptoms’	3.05%	2.44%	3.66%	±20%	Calculated [†] ; β	Soliman <i>et al.</i> [31] [§]
After laparoscopy:						
– To ‘laparoscopy #2’ from: ‘laparoscopy #1’ or ‘post-laparoscopy #1’	0.82%	0.65%	0.98%	±20%	Calculated [†] ; β	Soliman <i>et al.</i> [32] [¶]
– To ‘hysterectomy’ from: ‘laparoscopy #1 or #2’ or ‘post-laparoscopy #1 or #2’	1.43%	1.15%	1.72%	±20%	Calculated [†] ; β	Soliman <i>et al.</i> [32] [#]
– Other medical treatments (proportion)	19.6%	15.7%	23.6%	±20%	Calculated [†] ; β	Surrey <i>et al.</i> [33] ^{††}
– Operative death	0.003%	0.003%	0.038%	Low: -20%; hysterectomy high value	Calculated [†] ; β	Chapron <i>et al.</i> [34] ^{‡‡}
After hysterectomy:						
– Other medical treatments (proportion)	1.9%	1.5%	2.3%	±20%	Calculated [†] ; β	Surrey <i>et al.</i> [33] ^{††}
– Operative death	0.04%	0.03%	0.05%	±20%	Calculated [†] ; β	Mareh <i>et al.</i> [35] ^{§§}

[†]SE calculated as $(\text{base-low} + [\text{high-base}]) / (2 \times 1.96)$.

[‡]Cumulative recurrence rate of pain after DMPA treatment (12- adjusted to 3-month).

[§]Usage of surgical procedures following leuprolide acetate initiation for women with endometriosis (12- adjusted to 3-month).

[¶]Endometriosis-related laparoscopy (after 14 days of the first laparoscopy) occurring within 1 year of the first endometriosis-related laparoscopy (12- adjusted to 3-month).

[#]Endometriosis-related hysterectomy occurring within 1 year of the first endometriosis-related laparoscopy (12- adjusted to 3-month).

^{††}Medical treatment (gonadotropin-releasing hormone agonists, progestin and danazol) within 3 months of endometriosis-related laparoscopy or hysterectomy.

^{‡‡}Death from all types of laparoscopy (e.g., diagnostic, minor, major and advanced).

^{§§}Death within 6-week post-operative.

DSA: Deterministic sensitivity analysis; PSA: Probabilistic sensitivity analysis; SE: Standard error.

secondary osteoporosis, no alcohol 3 or more units/day, with a femoral neck BMD t-score of -1). In addition, as the weighted average age in EM-I and EM-II was 32 years (Table 1), 8 years younger than the minimum 40 years of age assumed for the FRAX score, the 10-year risk estimate of 0.1% was likely an overestimate. Combined with the facts that 1) neither treatments resulted in large incremental relative changes in BMD over 6 months (at most 5–6% decline for leuprolide acetate) [17,21,22,25,26]; 2) changes in BMD predominantly occurred while on treatment with partial recovery observed in the post-treatment follow-up studies [21,22,40]; and 3) model time horizon was only a maximum of 2 years, the impact of including versus excluding fractures on model results would likely be negligible.

Utilities

To estimate quality-adjusted life years (QALYs), utilities for the on- and off-treatment health states were derived from an analysis of patients' EQ-5D-5L data collected in EM-II at baseline, month 3 and month 6 (see Supplementary Material C). Utilities for the surgery states were derived using a similar approach as Roberts *et al.* [41]. Specifically, it was assumed that patients had zero utility for the first 3 days after a laparoscopy and the first seven days after a hysterectomy. Utilities for post-surgery states were assumed to be weighted averages of the utility for ‘other medical treatment with moderate/severe symptoms’ for the proportion of patients still experiencing symptoms and the utility for ‘off-treatment with no/mild symptoms’ for the remaining proportion of ‘cured’ patients after each type of surgery. Health state utilities in the model are summarized in Table 5 [41–43]. The AE- and surgical

Table 4. Treatment-related adverse event rates of any severity in the model.

3-month event rates	Base	Low	High	DSA info: low and high source	PSA info: SE used; assumed distribution	Source/note
Elagolix 150 mg QD (weighted average rates from Elaris EM-I and EM-II trial data): [37]						
– Breast pain	0.2%	0.2%	0.3%	±20%	Calculated [†] ; β	Include breast swelling/enlargement and tenderness
– Depression	1.3%	1.0%	1.5%	±20%	Calculated [†] ; β	Include depressed mood, depressive symptoms, emotional disorder
– Headache	6.8%	5.4%	8.1%	±20%	Calculated [†] ; β	Include migraines
– Hot flushes	12.8%	10.3%	15.4%	±20%	Calculated [†] ; β	Include night sweats
– Libido decrease	1.4%	1.1%	1.7%	±20%	Calculated [†] ; β	Include libido increased, loss of libido
– Nausea	5.4%	4.3%	6.5%	±20%	Calculated [†] ; β	Include vomiting
– Weight gain	1.2%	0.9%	1.4%	±20%	Calculated [†] ; β	Include weight decreased
Elagolix 200 mg BID (weighted average rates from Elaris EM-I and EM-II trial data): [37]						
– Breast pain	0.3%	0.3%	0.4%	±20%	Calculated [†] ; β	Include breast swelling/enlargement and tenderness
– Depression	2.8%	2.2%	3.3%	±20%	Calculated [†] ; β	Include depressed mood, depressive symptoms, emotional disorder
– Headache	9.0%	7.2%	10.8%	±20%	Calculated [†] ; β	Include migraines
– Hot flushes	27.7%	22.2%	33.3%	±20%	Calculated [†] ; β	Include night sweats
– Libido decrease	2.8%	2.2%	3.3%	±20%	Calculated [†] ; β	Include libido increased, loss of libido
– Nausea	6.7%	5.4%	8.1%	±20%	Calculated [†] ; β	Include vomiting
– Weight gain	1.2%	0.9%	1.4%	±20%	Calculated [†] ; β	Include weight decreased
Leuprolide acetate monotherapy (weighted average rates from leuprolide acetate PI): [17]						
– Breast pain	3.0%	2.4%	3.6%	±20%	Calculated [†] ; β	Include breast changes/tenderness
– Depression	12.8%	10.2%	15.4%	±20%	Calculated [†] ; β	Include emotional lability
– Headache	22.3%	17.8%	26.8%	±20%	Calculated [†] ; β	
– Hot flushes	64.1%	51.3%	76.9%	±20%	Calculated [†] ; β	Include hot sweats
– Libido decrease	5.7%	4.6%	6.8%	±20%	Calculated [†] ; β	
– Nausea	8.2%	6.5%	9.8%	±20%	Calculated [†] ; β	Include vomiting
– Weight gain	6.7%	5.3%	8.0%	±20%	Calculated [†] ; β	Include weight loss
Leuprolide acetate+NA (weighted average rates from leuprolide acetate PI): [17]						
– Breast pain	4.8%	3.9%	5.8%	±20%	Calculated [†] ; β	Include breast changes/tenderness
– Depression	17.5%	14.0%	21.0%	±20%	Calculated [†] ; β	Include emotional lability
– Headache	27.6%	22.1%	33.2%	±20%	Calculated [†] ; β	Include migraine
– Hot flushes	41.7%	33.3%	50.0%	±20%	Calculated [†] ; β	Include hot sweats
– Libido decrease	3.2%	2.6%	3.8%	±20%	Calculated [†] ; β	Include libido increase (changes)
– Nausea	9.0%	7.2%	10.9%	±20%	Calculated [†] ; β	Include vomiting
– Weight gain	3.5%	2.8%	4.2%	±20%	Calculated [†] ; β	Include weight loss
Surgical complications:						
– Laparoscopy	13.7%	10.9%	16.4%	±20%	Calculated [†] ; β	3-month results from Surrey et al. [33]
– Hysterectomy	25.1%	20.1%	30.1%	±20%	Calculated [†] ; β	3-month results from Surrey et al. [33]

[†]SE calculated as [(base-low) + (high-base)]/(2 × 1.96).

BID: Twice a day; DSA: Deterministic sensitivity analysis; NA: Norethindrone acetate; PI: Prescribing information; PSA: Probabilistic sensitivity analysis; QD: Once a day; SE: Standard error.

Table 5. Health state utilities in the model.

Health state utility	Base	Low	High	DSA info: low and high source	PSA info: SE used; assumed distribution	Source/note
Off-treatment with no/mild symptoms	0.842	0.674	1.000	±20%	Calculated [†] ; β	EQ-5D-5L data collected in elagolix Phase III trial Elaris EM-II (see Supplementary Material C) [§]
No/mild symptoms	0.874	0.699	1.000	±20%	Calculated [†] ; β	EQ-5D-5L data collected in elagolix Phase III trial Elaris EM-II (see Supplementary Material C) [§]
Moderate symptoms	0.777	0.622	0.933	±20%	Calculated [†] ; Log-normal	EQ-5D-5L data collected in elagolix Phase III trial Elaris EM-II (see Supplementary Material C) [§]
Severe symptoms	0.649	0.520	0.779	±20%	Calculated [†] ; Log-normal	EQ-5D-5L data collected in elagolix Phase III trial Elaris EM-II (see Supplementary Material C) [§]
Other medical treatment with moderate/severe symptoms	0.741	0.593	0.889	±20%	Calculated [†] ; Log-normal	EQ-5D-5L data collected in elagolix Phase III trial Elaris EM-II (see Supplementary Material C) [§]
Laparoscopy #1 and #2	0.689	0.551	0.827	±20%	Calculated [†] ; Log-normal	Abbott <i>et al.</i> [42] [¶]
Post-laparoscopy #1 and #2	0.822	0.658	0.987	±20%	Calculated [†] ; Log-normal	Assumed [#]
Hysterectomy	0.654	0.523	0.784	±20%	Calculated [†] ; Log-normal	Roberts <i>et al.</i> [41] [¶]
Post-hysterectomy	0.840	0.672	1.000	±20%	Calculated [†] ; Log-normal	Assumed [#]

[†]SE calculated as $((\text{base-low}) + (\text{high-base})) / (2 \times 1.96)$.

[‡]The relative difference (delta or ratio) in utility between these states and 'no/mild symptoms' were sampled from the log-normal distribution which was applied to obtain health utilities in these states at each simulation.

[§]Health state utilities were estimated using fractional logit GEE models.

[¶]For the hysterectomy and laparoscopy states, weighted average utilities of zero (0) utility for 7 and 3 days (assumed) followed by disutilities of 12.5% and 15.4% relative to the 'off-treatment with no/mild symptoms' state for ~84 and ~88 days, respectively, are assumed.

[#]Assumed to be weighted average of the utility of 'other medical treatment with moderate/severe symptoms' for the proportion of patients receiving other medical treatments and the utility of 'off-treatment with no/mild symptoms' for the remaining proportion of 'cured' patients after each surgery type.

DSA: Deterministic sensitivity analysis; GEE: Generalized estimating equation; PSA: Probabilistic sensitivity analysis; SE: Standard error.

Table 6. Adverse event and surgical complication disutilities in the model.

Adverse event disutility	Base	Low	High	DSA Info: low and high source	PSA info: SE used; assumed distribution	Source
Breast pain	-0.003	-0.002	-0.003	±20%	Calculated [†] ; β	Sullivan <i>et al.</i> [46] [‡]
Depression	-0.120	-0.096	-0.144	±20%	Calculated [†] ; β	Sapin <i>et al.</i> [45] [§]
Headache	-0.027	-0.022	-0.033	±20%	Calculated [†] ; β	Sullivan <i>et al.</i> [46] [¶]
Hot flushes	-0.011	-0.009	-0.014	±20%	Calculated [†] ; β	Lux <i>et al.</i> [44] [#]
Libido decrease	-0.049	-0.039	-0.059	±20%	Calculated [†] ; β	Maniadakis <i>et al.</i> [47] ^{††}
Nausea	-0.040	-0.032	-0.048	±20%	Calculated [†] ; β	Matza <i>et al.</i> [48] ^{‡‡}
Weight gain	-0.040	-0.032	-0.048	±20%	Calculated [†] ; β	Matza <i>et al.</i> [48] ^{§§}
Laparoscopy complication	-0.070	-0.056	-0.084	±20%	Calculated [†] ; β	Assumed same disutility as hysterectomy complication
Hysterectomy complication	-0.070	-0.056	-0.084	±20%	Calculated [†] ; β	Roberts <i>et al.</i> [41] ^{¶¶}

[†]SE calculated as $((\text{base-low}) + (\text{high-base})) / (2 \times 1.96)$.

[‡]Based on utility of nonmalignant breast conditions.

[§]Based on utility of mild depression.

[¶]Based on utility of headache including migraine.

[#]Based on the relative change in utility between no event versus weight gain, hot flushes, vaginal discharge.

^{††}Based on disutility of sexual dysfunction.

^{‡‡}Based on basic health state with nausea.

^{§§}Based on basic health state with 3% higher weight.

^{¶¶}Difference between hysterectomy (0.56) and severe complications after hysterectomy (0.49).

DSA: Deterministic sensitivity analysis; PSA: Probabilistic sensitivity analysis; SE: Standard error.

complication-related disutilities were either derived from published literature or assumed and summarized in Table 6 [41,44–48].

Table 7. Treatment acquisition and administration unit costs in the model.

Resource unit	Base ^{##} (2018 US\$)	Source/note
Elagolix (150 mg QD) – per mg	0.20	Red Book [®] Online [49] [†]
Elagolix (200 mg BID) – per mg	0.08	Red Book [®] Online [49] [‡]
Leuprolide acetate (11.25 mg/3-month IM injection) – per mg	326.52	Red Book [®] Online [49] [§]
NA (5 mg QD) – per mg	0.38	Red Book [®] Online [49] [¶]
DMPA (104 mg/3-month SC injection) – per injection	233.46	Red Book [®] Online [49] [#]
Danazol (300 mg BID) – per 200+100 mg capsule pair	10.02	Red Book [®] Online [49] ^{††}
Goserelin acetate (3.6 mg/month SC injection) – per injection	605.00	Red Book [®] Online [49] ^{‡‡}
Nafarelin acetate (0.2 mg nasal spray BID) – per nasal spray	35.46	Red Book [®] Online [49] ^{§§}
IM injection administration	31.32	CPT code: 96402 [50] ^{¶¶}
SC injection administration	20.88	CPT code: 96372 [50] ^{¶¶}

[†]Identifier(s): 00074-0038-28.
[‡]Identifier(s): 00074-0039-56.
[§]Identifier(s): 00074-3663-03.
[¶]Identifier(s): 65162-0475-09, 65162-0475-05, 65862-0715-50, 42291-0650-90, 50268-0602-15, 68462-0304-50, 00555-0211-10.
[#]Identifier(s): 00009-4709-13.
^{††}Identifier(s): 42291-0243-01, 00527-1369-01, 00527-1369-06, 00527-1368-01, 00555-0635-02, 00555-0635-09, 00555-0634-02.
^{‡‡}Identifier(s): 00310-0950-36.
^{§§}Identifier(s): 00025-0166-08.
^{¶¶}National non-facility.
^{##}The unit costs of treatment acquisition and administration were not varied in the DSA and PSA.
 BID: Twice a day; DMPA: Depot medroxyprogesterone acetate; DSA: Deterministic sensitivity analysis; IM: Intramuscular; NA: Norethindrone acetate; PSA: Probabilistic sensitivity analysis; QD: Once a day; SC: Subcutaneous; SE: Standard error.

Resource identification & costs

Each patient who spent a model cycle in the three on-treatment states incurred 3-month cost of acquiring and administering elagolix or leuprolide acetate ($\pm$ NA). Likewise, in every model cycle, each patient in the ‘other medical treatments with moderate/severe symptoms’ state and 19.6% (1.9%) of patients in the post-laparoscopy (post-hysterectomy) states incurred 3-month cost of acquiring and administering other medical treatments [33]. The 3-month cost of other medical treatments was assumed to be made up of progestin (62.8%; assumed to be DMPA), followed by GnRH agonists (36.6%; assumed to be equally distributed between goserelin and nafarelin acetate), and danazol (0.5%) [33].

Drug acquisition costs were calculated based on the drugs’ Wholesale Acquisition Cost prices and their [expected] indicated dose/frequency for endometriosis [49]. For elagolix, a price of US\$844.87 per 28-day was assumed for both doses. Administration costs were included for treatments administered intramuscularly (leuprolide acetate) and subcutaneously (DMPA and goserelin acetate) [50]. The unit costs behind their calculations are described in Table 7. Costs of managing treatment-related AEs, summarized in Table 8, were obtained from either the 2014 Medical Expenditure Panel Survey [51] or US-based published literature [52–55].

For non-surgery health states, direct medical costs were calculated as the sum product of the expected number of consultation and office visits with their unit costs [50,56]. For surgery states, direct medical costs of the surgery and 3-month post-surgical healthcare were obtained from the 3-month results of a US claims database study on the cost burden of endometriosis surgeries [57]. The 3-month post-surgical healthcare costs covered amounts paid for inpatient admissions, emergency room, outpatient visits and outpatient pharmacy. Finally, patients in the operative death state incurred a one-time cost, assumed to be the same as the average hospitalization cost for uterine endometriosis [58]. These direct medical costs and utilization are presented in Table 9.

Unit costs of resources were inflated to 2018 US\$ using the medical component of the consumer price index [59] and adjusted to 3-month costs [29]. Unit costs of resources obtained from published cost databases were not varied in sensitivity analysis; only cost estimates from statistical analyses were varied.

Discounting

Both costs and benefits were discounted at a rate of 3% per year (equivalent to a 3-month rate of 0.74%), which was varied from 0 to 7% per annum in sensitivity analyses [60].

Table 8. Adverse event 3-month management costs in the model.

Adverse event	Base (2018 US\$)	Low (2018 US\$)	High (2018 US\$)	DSA info: low and high source	PSA info: SE used; assumed distribution	Source/note
Breast pain	394	316	473	±20%	Calculated [†] ; γ	MEPS (2014) [51] [‡]
Depression	611	489	734	±20%	Calculated [†] ; γ	MEPS (2014) [51] [§]
Headache	251	200	301	±20%	Calculated [†] ; γ	MEPS (2014) [51] [¶]
Hot flushes	363	290	436	±20%	Calculated [†] ; γ	Sarrel <i>et al.</i> [53]
Libido decrease	279	223	334	±20%	Calculated [†] ; γ	Foley <i>et al.</i> [52] [#]
Nausea	110	88	132	±20%	Calculated [†] ; γ	Piwko <i>et al.</i> [54] ^{††}
Weight gain	526	421	631	±20%	Calculated [†] ; γ	Kim <i>et al.</i> [55] ^{‡‡}

[†]SE calculated as $([\text{base-low}] + [\text{high-base}]) / (2 \times 1.96)$.

[‡]MEPS mean expenses per person with care (any service) for non-malignant breast disease.

[§]MEPS mean expenses per person with care (any service) for mental disorders.

[¶]MEPS mean expenses per person with care (any service) for headache.

[#]Increase in 12-month total costs between women diagnosed with sexual dysfunction and matched controls.

^{††}Direct cost per woman treated for moderate nausea and vomiting of pregnancy (assume 3-month costs).

^{‡‡}Annual medical spending attributable to an obese individual in 2014 US\$.

DSA: Deterministic sensitivity analysis; MEPS: Medical Expenditure Panel Survey; PSA: Probabilistic sensitivity analysis; SE: Standard error.

Sensitivity analyses

Deterministic sensitivity analysis (DSA) was conducted by varying model parameters by their low and high values (presented in Tables 1–9) to assess their impact on model outputs. DSA results are presented in the form of tornado diagrams for a given payer's willingness-to-pay (WTP) for a QALY (assumed to be US\$100,000/QALY). Probabilistic sensitivity analysis (PSA) was conducted by considering the uncertainty in all model parameters simultaneously. Results are presented as cost–effectiveness acceptability curves (CEAC; i.e., probability of each treatment option being cost–effectiveness for a given WTP threshold).

Results

Base case results of the model are presented in Table 10 for the 1- and 2-year time horizons. Over the 1-year time horizon, both doses of elagolix dominated leuprolide acetate, in other words, elagolix generated more QALYs for less costs. Compared with leuprolide acetate, both doses of elagolix generated positive net monetary benefit (NMB) based on a payer WTP of US\$100,000/QALY over the 1-year time horizon: US\$5660 for 24-month elagolix 150 mg QD and US\$6443 for 6-month elagolix 200 mg BID. Similarly, over the 2-year time horizon, both doses of elagolix were associated with positive NMBs relative to leuprolide acetate: US\$2374 for 24-month elagolix 150 mg QD and US\$1342 for 6-month elagolix 200 mg BID.

Figures 2 and 3 present the results of the DSA showing the ten most influential model parameters. Over the 1-year time horizon, the model was most sensitive to the non-surgery health state utilities, the treatment-specific response rates for NMPP and DYS, as well as the AE-related disutilities. In all the DSA runs, both 24-month elagolix 150 mg QD and 6-month elagolix 200 mg BID remained cost-effective versus leuprolide acetate based on a WTP of US\$100,000/QALY, indicating robust 1-year model outcomes. Over the 2-year time horizon, the model was likewise most sensitive to the non-surgery health state utilities and the treatment-specific response rates for NMPP and DYS. The comparison of 24-month elagolix 150 mg QD versus leuprolide acetate revealed that elagolix was strictly cost-effective versus leuprolide acetate in eight of the ten most influential parameters at a WTP of US\$100,000/QALY (Figure 3A). This fell to five out of ten influential parameters for 6-month elagolix 200 mg BID versus leuprolide acetate (Figure 3B).

Figure 4 (A–D) present the CEACs of the 500 PSA simulations. Over the 1-year time horizon, both 24-month elagolix 150 mg QD (A) and 6-month elagolix 200 mg BID (B) were the cost-effective option versus leuprolide acetate in 100% of the PSA simulations, for any WTP up to US\$100,000/QALY. When the time horizon was extended to 2 years, the probabilities of 24-month elagolix 150 mg QD (C) and 6-month elagolix 200 mg BID (D) being cost-effective versus leuprolide acetate were 80.2 and 78.4%, respectively, for a WTP threshold of US\$100,000/QALY.

Discussion

The CEM showed that both elagolix regimens (i.e., 24-month 150 mg QD and 6-month 200 mg BID) were cost-effective versus leuprolide acetate over the 1-year time horizon, generating positive NMBs versus leuprolide

Table 9. Direct medical costs and utilization by health state in the model.

Cost component	Base	Low	High	DSA info: low and high source	PSA info: SE used; assumed distribution	Source/note
Unit costs of outpatient visits (2018 US\$):						
– Consultation visit for a new patient	150			Not varied	Not varied	CPT code: 99204 [50]
– Office visit for an established patient	63			Not varied	Not varied	CPT code: 99213 [50]
Non-surgery health states: Number of consultation visit(s) per 3-month:						
– Off-treatment with no/mild symptoms	0.0	0.00	1.00	±1 (min 0)	Calculated [†] ; γ	Assumed
– No/mild symptoms	0.5	0.00	1.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 0.5 initial visit per quarter based on Winkel <i>et al.</i> [56]
– Moderate symptoms	0.5	0.00	1.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 0.5 initial visit per quarter based on Winkel <i>et al.</i> [56]
– Severe symptoms	0.5	0.00	1.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 0.5 initial visit per quarter based on Winkel <i>et al.</i> [56]
– Other medical treatment with moderate/severe symptoms	0.5	0.00	1.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 0.5 initial visit per quarter based on Winkel <i>et al.</i> [56]
– Post-laparoscopy #1 and #2	0.0	0.00	1.00	±1 (min 0)	Calculated [†] ; γ	Post-surgical states; assumed
– Post-hysterectomy	0.0	0.00	1.00	±1 (min 0)	Calculated [†] ; γ	Post-surgical states; assumed
Non-surgery health states: number of office visit(s) per 3-month:						
– Off-treatment with no/mild symptoms	0.0	0.00	1.00	±1 (min 0)	Calculated [†] ; γ	Assumed
– No/mild symptoms	1.5	0.50	2.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 1.5 return visit per quarter based on Winkel <i>et al.</i> [56]
– Moderate symptoms	1.5	0.50	2.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 1.5 return visit per quarter based on Winkel <i>et al.</i> [56]
– Severe symptoms	1.5	0.50	2.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 1.5 return visit per quarter based on Winkel <i>et al.</i> [56]
– Other medical treatment with moderate/severe symptoms	1.5	0.50	2.50	±1 (min 0)	Calculated [†] ; γ	On-treatment states; assumed 1.5 return visit per quarter based on Winkel <i>et al.</i> [56]
– Post-laparoscopy #1 and #2	1.0	0.00	2.00	±1 (min 0)	Calculated [†] ; γ	Post-surgical states; assumed
– Post-hysterectomy	0.0	0.00	1.00	±1 (min 0)	Calculated [†] ; γ	Post-surgical states; assumed
Surgery health states: surgery and 3-month post-surgical healthcare costs (2018 US\$):						
– Laparoscopy	11,765	11,677	11,852	Published $\pm 1.96 \times \text{SE} = \text{US\$45}$	γ	3-month results from Soliman <i>et al.</i> [57]
– Hysterectomy	16,155	16,044	16,267	Published $\pm 1.96 \times \text{SE} = \text{US\$57}$	γ	3-month results from Soliman <i>et al.</i> [57]
– Operative death (one-time cost)	10,563	10,056	11,070	Published $\pm 1.96 \times \text{SE} = \text{US\$259}$	γ	HCUPnet [58] [‡]
[†] SE calculated as $([\text{base-low}] + [\text{high-base}]) / (2 \times 1.96)$. [‡] Average hospitalization cost for uterine endometriosis (International Classification of Diseases, 9th Revision, code 617.0). DSA: Deterministic sensitivity analysis; PSA: Probabilistic sensitivity analysis; SE: Standard error.						

acetate at a WTP of US\$100,000/QALY. In fact, base case results showed that both elagolix regimens dominated leuprolide acetate, generating more benefits (i.e., QALYs) for less costs. These results were robust to extensive sensitivity analyses. Specifically, the DSA showed that positive NMB was maintained for both elagolix regimens despite wide ranges (mostly $\pm 20\%$) in model inputs. Likewise, the PSA revealed that the dominance of 24-month 150 mg QD over leuprolide acetate was robust, occurring in 99.6% of 500 simulations. The dominance of 6-

Table 10. Base case model results for 1- and 2- year time horizons.

Treatment	Total costs (2018 US\$)	Δ Costs vs LA (2018 US\$)	Total QALYs	Δ QALY vs LA	ICER vs LA (2018 US\$)	NMB vs LA (2018 US\$) [†]
1-year time horizon results						
Elagolix (150 mg QD) for 24 months	12,202	-4482	0.7414	0.0118	Elagolix dominant	5660
Elagolix (200 mg BID) for 6 months	10,551	-6132	0.7327	0.0031	Elagolix dominant	6443
LA (+NA) for 12 months	16,683	–	0.7296	–	–	–
2-year time horizon results						
Elagolix (150 mg QD) for 24 months	21,017	-591	1.5005	0.0178	Elagolix dominant	2374
Elagolix (200 mg BID) for 6 months	17,833	-3775	1.4583	-0.0243	155,145 (for LA)	1342
LA (+NA) for 12 months	21,607	–	1.4827	–	–	–

[†]NMB determined based on a payer WTP of US\$100,000 per QALY.
 BID: Twice daily; ICER: Incremental cost–effectiveness ratio; LA: Leuprolide acetate; NMB: Net monetary benefit; QALY: Quality-adjusted life year; QD: Once a day; WTP: Willingness-to-pay.

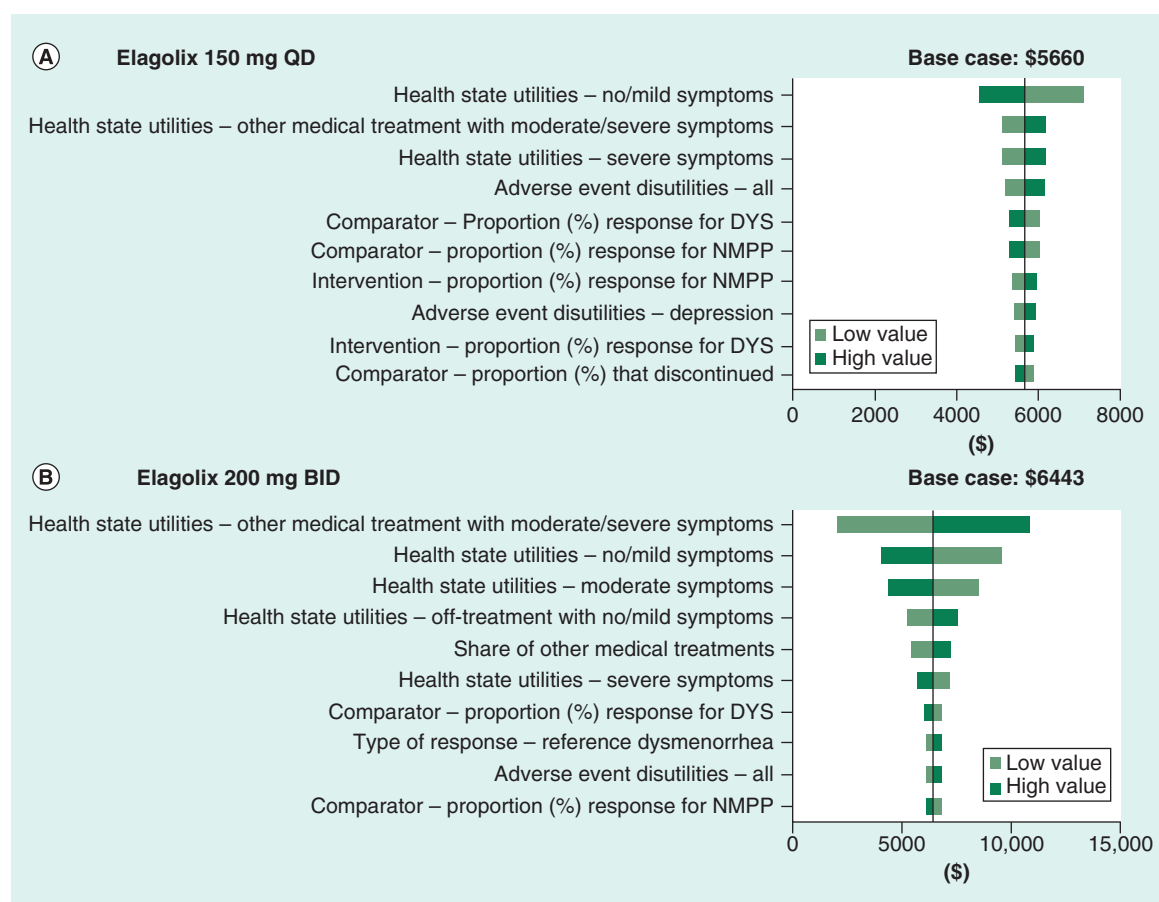


Figure 2. Deterministic sensitivity analysis results showing the ten most influential model parameters comparing elagolix 150 mg once a day and elagolix 200 mg twice a day to leuprolide acetate: 1-year net monetary benefit (willingness-to-pay = US\$100,000/quality-adjusted life year). A dotted vertical line indicating an net monetary benefit of zero based on a willingness-to-pay of US\$100,000/quality-adjusted life year is displayed. Hence, bars strictly to the right of this line indicate sensitivity analyses where elagolix is cost-effective against leuprolide acetate.
 BID: Twice a day; DYS: Dysmenorrhea; NMPP: Nonmenstrual pelvic pain; QD: Once a day.

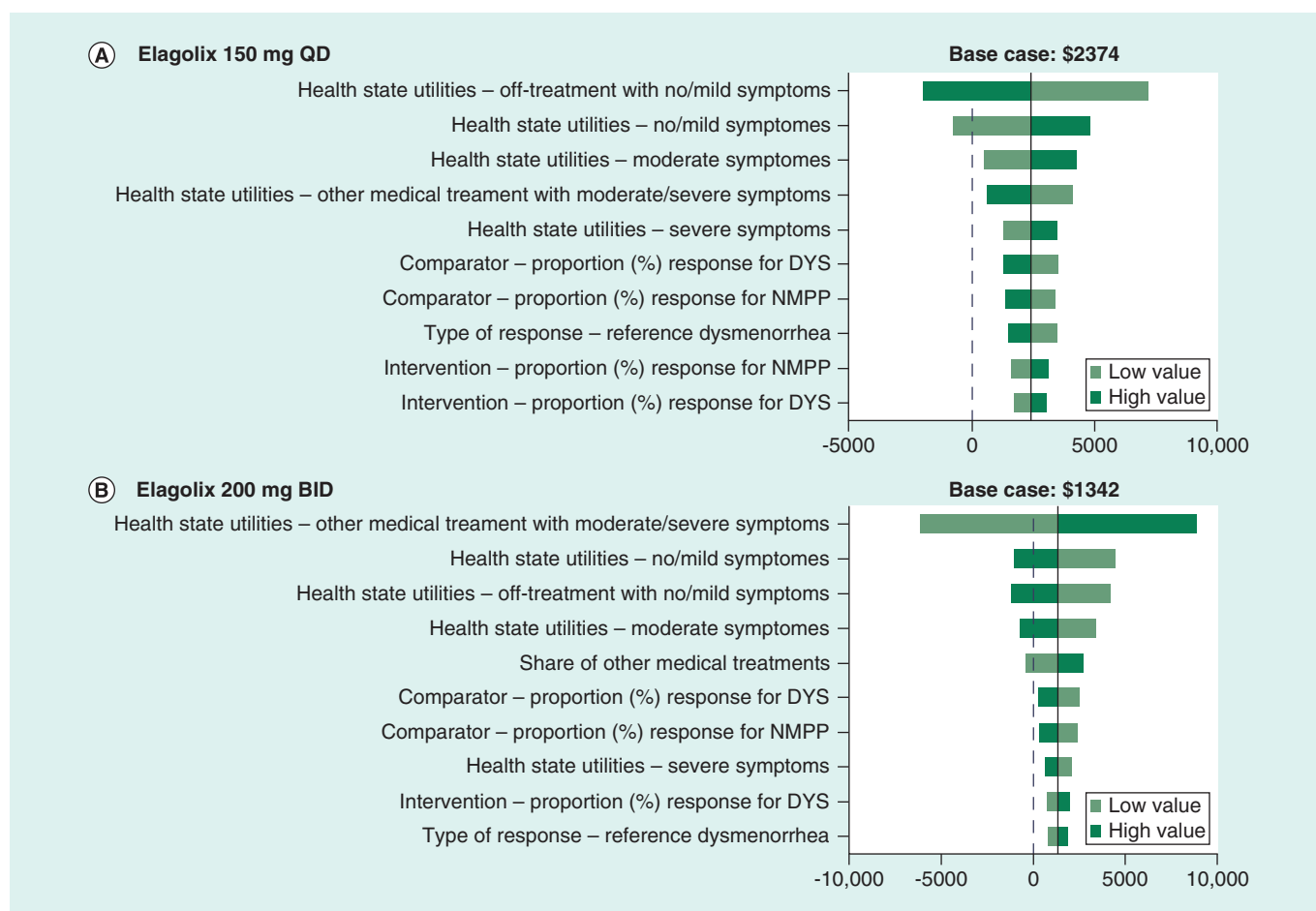


Figure 3. Deterministic sensitivity analysis results showing the ten most influential model parameters comparing elagolix 150 mg once a day and elagolix 200 mg twice a day to leuprolide acetate: 2-year net monetary benefit (willingness-to-pay = US\$100,000/adjusted life year). A dotted vertical line indicating a net monetary benefit of zero based on a willingness-to-pay of US\$100,000/quality-adjusted life year is displayed. Hence, bars strictly to the right of this line indicate sensitivity analyses where elagolix is cost-effective against leuprolide acetate.

BID: Twice a day; DYS: Dysmenorrhea; NMPP: Nonmenstrual pelvic pain; QD: Once a day.

month 200 mg BID over leuprolide acetate was less robust, occurring in 64.0% of 500 simulations, due to greater variability in elagolix's ability to generate more QALYs than leuprolide acetate.

The cost-effectiveness of elagolix versus leuprolide acetate was maintained when extending the time horizon from 1 to 2 years, albeit at reduced magnitudes. Over the 2-year time horizon, the 24-month 150 mg QD regimen generated a positive NMB, indicating that it continued to be cost-effective versus leuprolide acetate but at a more marginal NMB (US\$2374). Similarly, the 6-month 200 mg BID regimen generated a smaller NMB (US\$1342). These base case results appeared to be highly sensitive: the DSA showed that wide range (mostly $\pm 20\%$) changes in key model inputs such as non-surgery health state utilities would switch the NMB of both elagolix regimens from positive to negative or vice versa. The highly sensitive nature of the 2-year model results was also supported by the scatterplots and CEACs of the PSA.

The 1-year model results were more appropriate indicators of elagolix's value in the current context where the treatment duration in EM-I and EM-II trials was for 6 months, treatments had unequal model DOTs (i.e., 6-month elagolix 200 mg BID vs 12-month leuprolide acetate), and there were no expected benefits and harms of therapy once discontinued. As such, the shorter time horizon minimized the reliance on extrapolated trial results, reduced the impact of unequal model DOTs and simplified the model to capture differential benefits and harms of treatments only when present, respectively. Longer time horizons would have been more appropriate if there

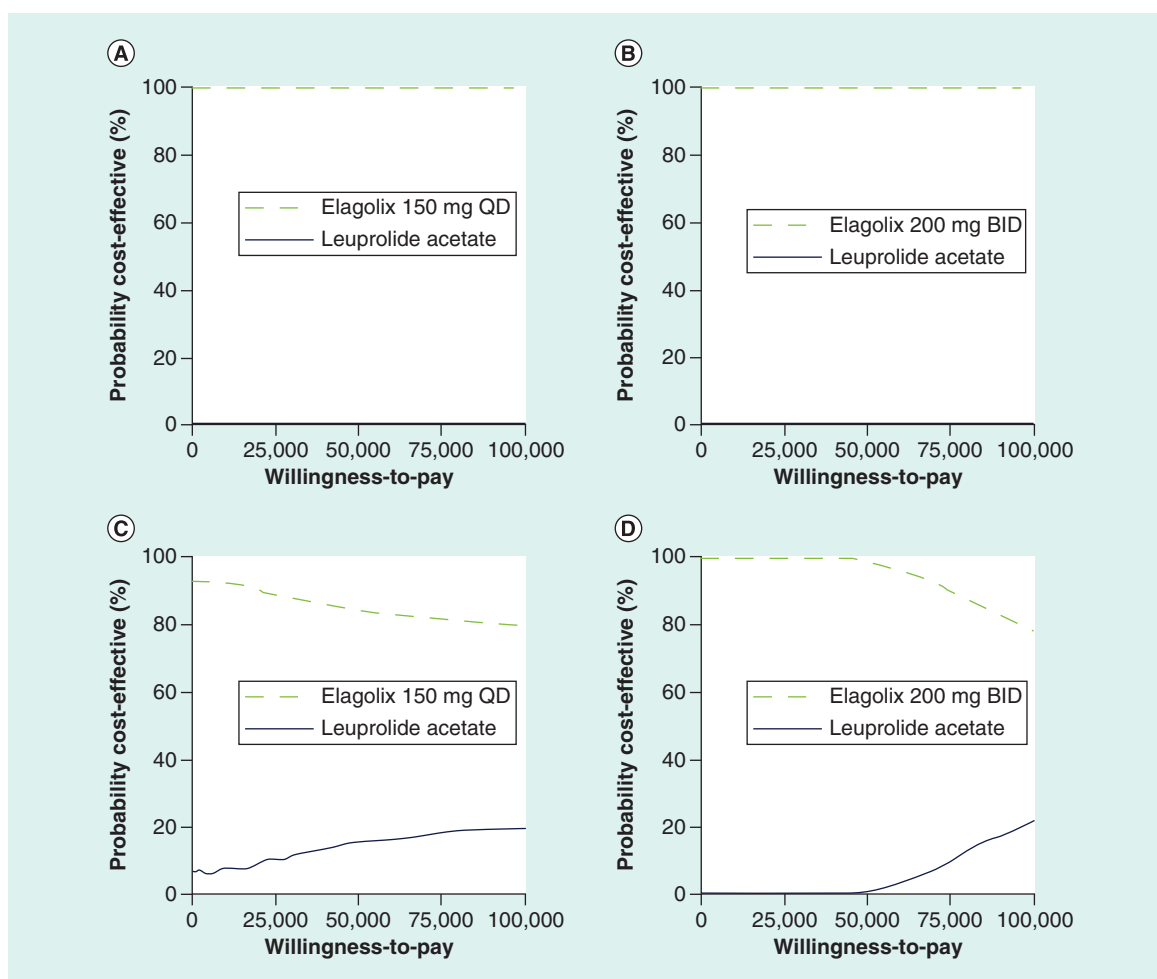


Figure 4. Probabilistic sensitivity analysis; results, cost-effectiveness acceptability curve. (A) Elagolix 150 mg once a day and leuprolide acetate: 1-year; **(B)** elagolix 200 mg twice a day and leuprolide acetate: 1-year; **(C)** elagolix 150 mg once a day and leuprolide acetate: 2-year; **(D)** elagolix 200 mg BID and leuprolide acetate: 2-year. BID: Twice a day; QD: Once a day.

were a persistent differential in mortality or morbidity from two or more treatments for a disease, which is not the expectation for endometriosis.

The cost-effectiveness of treatments for endometriosis pain symptoms has been studied earlier by the NIH and Care Excellence (NICE) in the UK [61], Wu *et al.* [62], Sanghera *et al.* [63], as well as the previously mentioned ICER review of elagolix [23]. However, none of these previous studies are relevant to the present study. The NICE review used a Markov decision analytic model to assess the cost-effectiveness of various combinations of diagnostic and treatment strategies over a lifetime [61]. As such, a 'population of healthy women' entered the NICE model, while a population of women with surgically-diagnosed endometriosis entered the current model. Wu *et al.* [62] and Sanghera *et al.* [63] are likewise irrelevant as both studies are economic evaluations of different strategies to prevent endometriosis recurrence following conservative surgery. This means that all patients entered their models without endometriosis symptoms, which is in direct contrast to the moderate to severe endometriosis pain experienced by patients entering the current model.

One scenario not considered owing to lack of data was that the model did not incorporate formulation preferences and their effect on quality-of-life, such as the preference women with endometriosis have for daily oral dosing over monthly injections [64]. Another scenario not included due to negligible impact on model results was the treatments' effect on BMD loss. Though statistically significant losses in BMD were observed in both treatments' clinical trials [17,21,22,25,26,40], owing to the low-risk study population (by average age) and short model time horizons (1- and 2-year), these losses did not translate into meaningful absolute and incremental fracture risks.

The risk of cardiovascular symptoms (such as palpitations, syncope and tachycardia) in women with endometriosis treated with Lupron was observed in less than 5% of subjects in the Lupron trials [17]. Both favorable changes (i.e., increase in high-density lipoprotein cholesterol [HDL-C]) and unfavorable changes (i.e., increase in low density lipoprotein cholesterol [LDL-C]) in lipid profile were observed in patients treated with elagolix [21,22]. However, it is unclear whether these changes in lipid profile would affect long-term cardiovascular risk in this otherwise low-risk population [22]. Like BMD, cardiovascular risk was not included in the model, owing to the short time horizon of the analysis. Moreover, the lower rates of its occurrence also meant that its absolute and incremental impact would be negligible.

The CEM was subject to several other key limitations. First, no head-to-head trial compared the two therapies. Second, the elagolix and leuprolide acetate trials included different end points for assessing efficacy. As such, the efficacy of the comparator leuprolide acetate in the model needed to be predicted using elagolix Phase III data instead of taken as observed. Third, the model was based on clinical trial results for efficacy and AE rates, but real-world outcomes would be more appropriate to estimate effects; at this time, there are no real-world outcomes for elagolix-treated patients. Fourth, AE data may not be reported similarly across the elagolix and leuprolide acetate trials, and health utilities and cost estimates came from AEs measured in other studies. Health utility was not measured frequently enough in the elagolix studies to validly identify AE disutilities in an endometriosis patient population. Finally, the model evaluated average effects for all indicated patients; subgroup analysis was not conducted owing to lack of data, but effects could be different across patient subgroups.

Conclusion

The base case and sensitivity results of the CEM showed that the two recently FDA-approved doses of elagolix for the management of moderate to severe pain associated with endometriosis – namely 24-month 150 mg QD and 6-month 200 mg BID – were both cost-effective versus leuprolide acetate over a time horizon of 1 to 2 years. Our results were robust to sensitivity analyses. Moreover, treatment with elagolix is an oral medication, which may be favorable to surgery or intramuscular injection treatment alternatives. Last, given that the burden of endometriosis in the US is significant, elagolix seems to offer a good value for money treatment option for payers.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://www.futuremedicine.com/doi/suppl/10.2217/cer-2018-0124>

Author contributions

AM Soliman, SK Agarwal, SJ Johnson, S-T Wang and D Mitchell were involved in the conception and design of the analysis; S-T Wang and D Mitchell were involved in the analysis and interpretation of the data; all authors were involved in revising it critically for intellectual content; and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Financial & competing interests disclosure

S-T Wang and SJ Johnson are employees of Medicus Economics LLC, a consulting company that conducts economic evaluations in a variety of therapeutic areas for pharmaceutical companies, which received payment from AbbVie, the study sponsor. D Mitchell is a contractor to Medicus Economics. AM Soliman and JB Vora are employees of AbbVie Inc. and may own AbbVie stock. AbbVie is the manufacturer of elagolix and Lupron Depot (leuprolide acetate). SK Agarwal has served in a consulting role on research for AbbVie Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Data sharing statement

The authors certify that this manuscript reports the secondary analysis of clinical trial data that have been shared with them, and that the use of this shared data is in accordance with the terms (if any) agreed upon their receipt. The source of these data is: NCT01620528 and NCT01931670.

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Summary points

- Endometriosis is a chronic gynecological condition with an estimated prevalence ranging from 4 to 10% among women in their reproductive years.
- Endometriosis manifests with pain symptoms that are often severe enough to result in decrements in quality-of-life and productivity in the workplace and at home.
- In July 2018, elagolix (ORILISSA™) became the first and only US FDA-approved oral gonadotropin-releasing hormone (GnRH) antagonist for treating moderate to severe endometriosis pain. There are two approved regimens of elagolix: 150 mg once daily (QD) for 24 months or 200 mg twice daily (BID) for 6 months.
- This study assessed the 1- and 2-year cost-effectiveness of both elagolix regimens, relative to 12-month leuprolide acetate plus 6-month add-back, for moderate to severe endometriosis pain from a US payer perspective.
- A *de novo* Markov state transition model was developed that tracked and quality-adjusted the time spent in treatment, off treatment, surgery, post-surgery and death by a hypothetical cohort of endometriosis patients in 3-month increments.
- Model inputs were obtained from Phase III trials data and published literature.
- Due to efficacy measurement differences across treatments, the efficacy of leuprolide acetate was mapped from its trial patient characteristics using statistical prediction models estimated from the elagolix patient-level Phase III data.
- Model results showed that elagolix was cost-effective versus leuprolide acetate in the management of moderate to severe endometriosis pain over 1- and 2-year time horizons, generating positive net monetary benefits at a willingness-to-pay of US\$100,000/quality-adjust life year.
- Model results were robust to both deterministic and probabilistic sensitivity analyses.
- Elagolix may be considered a cost-effective treatment option in women with moderate to severe endometriosis pain from a US healthcare payer perspective.

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