INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Elagolix for Treating Endometriosis

Response to Public Comments on Draft Evidence Report

June 15

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1.	***Manufacturers***	
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3.	**ICER's rating on the comparative net health benefit of elagolix should be revised** • ICER assigns a rating of P/I (promising but inconclusive) for the comparative net health benefit of elagolix versus placebo (Table 3.12). AbbVie disagrees with this rating based on the strong evidence for the efficacy and safety of elagolix for endometriosis. o The Elaris Endometriosis I and II (EM-I and EM-II)1,2 trials are the largest to date to study endometriosis and its treatments, and have been judged to be of good quality by ICER (page 22). Even in the Phase II trials (e.g., Tulip-PETAL3 and Lilac-PETAL4) that used slightly different efficacy measures, significant benefits of elagolix versus placebo were observed. o Significant benefits were observed comparing elagolix versus placebo across several outcome measures (i.e., dysmenorrhea [DYS] response, non-menstrual pelvic pain [NMPP] response, secondary pain outcomes, quality of life and analgesic use) in the pivotal Phase III trials Elaris Endometriosis I and II (EM-I and EM-II).1,2 o There were no significant differences in serious or severe adverse events (AEs) between the elagolix and placebo arms in the EM-I and EM-II trials.1 In addition, elagolix is not associated with a sustained reduction in bone mineral density (BMD), an hypoestrogenic-induced AE, after treatment discontinuation. In the long-term extension studies EM-III and EM-IV, lumbar spine, hip and femoral neck BMD assessments showed progressive recovery towards baseline and Z-scores remained within normal values for age-matched population during the post-treatment follow-up period.5,6 Further, short-term BMD loss does not correlate one-to-one with increased fracture risk; prior research has found that the overall proportion of fractures attributable to low BMD is modest.7,8	The ICER rating of P/I is based upon a review of all available Phase II and III studies involving elagolix and the clinical context provided by experts as well as patient and patient advocate input. Endometriosis is recognized as a chronic condition for which there is currently no cure. Patients and clinicians have a number of different treatment options, but none offers long-term benefit. Thus, data from short-term trials needs to be assessed in this context. Data from available Phase II and III studies demonstrate a short-term, dose dependent improvement in symptoms for elagolix compared to placebo. However, long-term comparative data is lacking to assess whether ongoing use of elagolix would continue to be beneficial in early responders. Similarly, though short-term safety data is what would be expected with ovarian hormone suppression, the long-term safety of elagolix remains to be established. For this reason, a "promising, but inconclusive" rating is recommended. Finally, the FDA notification postponing its decision on elagolix while awaiting further information about liver related toxicity, something not noted in published data, raises additional concerns beyond those previously noted.

4.	**The elagolix 150 mg QD dose should be considered. Only elagolix 200 mg twice daily (BID) is considered in ICER's economic evaluations.** However, two different doses were evaluated in the EM-I and EM-II clinical trials, i.e., 150 mg once daily (QD) and 200 mg BID, and both were submitted to the FDA for review. AbbVie recommends that ICER consider both elagolix doses in its economic evaluations.	We engaged clinicians during our scoping period to help us determine if we should model both doses, or only one dose. Clinicians indicated they were likely to maximally dose for effectiveness, while of course monitoring for adverse events. Therefore, based on this stakeholder feedback, we modeled the 200mg dose to best represent real-world practice. Furthermore, given the delay in FDA approval, the price and approved dosing remains unknown.
5.	**A maximum duration of continuous elagolix treatment should be considered.** ICER's cost-effectiveness (CE) model assumes that patients in the reduced pain state use elagolix continuously until pain recurrence, surgery, or pregnancy. By not limiting the elagolix treatment duration, ICER's evaluation could lead to a model in which women may still be on elagolix treatment after 18 years. This is unlikely be to the case in clinical practice.	We recognize that it is unlikely for all patients to continue elagolix treatment for an 18 year period. However, during our scoping process, we received feedback from stakeholders regarding patients taking hormonal therapies. We heard that while the indication may be for a shorter period of time, doctors often work with their patients to continue taking prescribed treatment if the treatment is effective at reducing endometriosis-related pain. Further, we assumed that continued treatment response in the reduced pain state was associated with elagolix treatment. That is, patients discontinue for various reasons, and thus, they would only still be on treatment for 18 years if they were continually responding. Therefore, improved health outcomes track alongside increased costs related to elagolix treatment.
6.	**Elagolix for dysmenorrhea and non-menstrual pelvic pain should be modeled together. ICER evaluates elagolix in separate CE models for the DYS and NMPP outcomes.** AbbVie does not think this is an appropriate way to model endometriosis outcomes and recommends that ICER update the model to evaluate both response measures together in the same model, using reasonable assumptions to weigh and combine the two response measures as needed. First, endometriosis is coded as one disease with an ICD-10 code of N80.X, with the X specifying the location of the endometriosis and not the pain symptom. As such, the clinical reality is that endometriosis-related DYS and NMPP are treated as one disease. Second, evaluating the two pain symptoms separately underestimates the value of elagolix treatment. In a given month, patients could experience DYS during their menstrual period and NMPP during the rest of the month, such that they could garner treatment benefits for both pain symptoms over the month. Therefore, an	This modeling framework was used in the draft report for two reasons: 1) response to dysmenorrhea-related pain and nonmenstrual pelvic pain are correlated outcomes, and without patient-level data, we were not able to aggregate these effects; 2) the numeric pain rating scale was not reported separately for dysmenorrhea-related pain and nonmenstrual pelvic pain. Therefore, mapping to a utility score by specific pain symptom was not possible. We've taken AbbVie's feedback--and others--and integrated a weighted average response metric into the revised report. With no access to patient-level data, we calculated a weighted average of response based on an average menstrual cycle duration. Specifically, response to dysmenorrhea trial evidence was applied to an average proportion of time of menstruation within each model cycle. Response to nonmenstrual pelvic pain was applied to the remaining proportion of time within each model cycle to estimate an average combined measure of response. For any given measurement day, a patient is not experiencing both the menstrual and

	evaluation of elagolix for DYS alone captures only a portion of its value over a month and vice versa for an evaluation of elagolix for NMPP alone. Indeed, only by evaluating DYS and NMPP together could a model capture 100% of the value of elagolix. Finally, the fact that DYS and NMPP are symptoms of one disease is further reflected in one of the inclusion criteria to the elagolix Phase III trials EM-I and EM-II: patients were required to have at least 2 days of moderate or severe DYS and NMPP during that last 35 days in the screening period.	non-menstrual part of their cycle. This measure is reflective of not requiring all days to achieve response, but on any selected day. Given that most of the patient's time is spent in a nonmenstrual state, this weighted average is closer to the nonmenstrual pelvic pain treatment response rates. Menstruation duration was assumed the same between elagolix and placebo, but was varied across a wide range in sensitivity analyses to account for uncertainty and variation. The combined response was used to assess long-run costs and outcomes of treatment with elagolix and the comparator.
7.	**Receipt of add-on treatment(s) following surgery should be considered.** In ICER's model, women in post-surgery health states would not receive any active add-on treatment except for analgesics. AbbVie does not believe this reflects the real-world treatment patterns for endometriosis and suggests that ICER allow receipt of additional add-on treatment(s) for the post-surgery states to be more aligned with real-world treatment patterns for endometriosis. The ASRM guideline recommends medical add-on therapy using hormonal therapies (e.g., GnRH inhibitors, combined oral contraceptives) following the surgical procedures to prolong the benefits of surgery and manage symptoms. The recommended duration for the add-on treatment is 6 months. Surrey et al. 2017 reported that 25.2%, 11.6% and 22.8% of patients used combined oral contraceptives, GnRH agonists, and progestin, respectively, within 12 months after undergoing laparoscopy; and 1.0%, 0.5%, and 3.0% of patients used combined oral contraceptives, GnRH agonists, and progestin, respectively, within 12 months after undergoing hysterectomy.	We have added the cost of add-back therapy to the model. Specifically, a proportion of women in all post-surgery states were assumed to incur the cost of leuprolide and combined oral contraceptive add-back therapy based on prior evidence of add-back therapy use. After surgery, the model was flexible and allowed for a proportion to respond with reduced pain and for the remaining proportion to not respond to surgery. Because a repeat and final surgery (i.e., hysterectomy and bilateral oophorectomy) could occur, the model accounted for women who potentially responded to final surgery with reduced pain or those who did not respond to final surgery and continued with moderate-to-severe pain. Note, with regards to your comment, that women in reduced pain states incurred costs for analgesics at half the cost (assumed) of those in the moderate to severe pain 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 treatment.
8.	**Probability of hysterectomy without prior laparoscopy should be considered.** ICER assumes that hysterectomy could only occur as a repeat (i.e., after laparoscopy) and final surgery. However, in the real world, patients may have hysterectomy without prior laparoscopy. Per Table 3 of Soliman et al. 2016, 11.7% of patients received hysterectomy in the one-year following leuprolide acetate treatment, while only 4.2% received laparoscopy, suggesting that some patients received	While we recognize that some women may have hysterectomy without prior laparoscopy, the Soliman et al. 2016 article used subsequent surgery rates post-laparoscopic surgery plus the use of leuprolide acetate treatment, among other treatment options. That is, any type of endometriosis-related surgery was an inclusion criteria of the Soliman et al. 2016 article. Furthermore, evidence from other publications (see Fuldeore et al. 2011) suggested therapeutic laparoscopic surgery was the most

	hysterectomy without prior laparoscopy. As such, AbbVie recommends that ICER include the probability of hysterectomy without prior laparoscopy in the model.	common procedure performed (32% vs. 22.1% abdominal hysterectomy and 6.8% vaginal hysterectomy) among over 15,000 women with endometriosis in the United States. In addition, model findings are in line with these evidence-based surgery rates.
9.	**Recurrence of pain symptoms after successful surgery should be considered.** ICER assumes that women who experienced successful surgery enter the post-surgery with reduced pain (M4) state and remain there indefinitely. However, this is not consistent with real-world observations, where recurrence of pain symptoms after surgery is not insignificant.12-16 This issue is exacerbated with the long model time horizon.	Pain symptoms are assessed during the 3-month "tunnel state" of surgery. Once women respond or do not respond to surgery, they move to a reduced pain state or a continued moderate to severe pain state. Therefore, the model allows for patients to not respond to surgery. The majority of literature available lists 3 to 6-month response rates for treatments and surgeries. Given a lack of evidence on long-run recurrence rates, we assumed patients that responded during the 3-month tunnel state would respond indefinitely, but still use pain agents to assist with any remaining pain. Furthermore, we've now included the cost of add-back therapy to post-surgery states to better align with evidence on repeat surgeries.
10.	More comprehensive surgical procedure unit costs should be considered • Per Table F2, the unit costs for laparoscopic surgery and hysterectomy per event used in the model were $5,433 and $14,437, respectively, based on Fuldeore et al. 2011.17 AbbVie believes the current inputs underestimate the surgery cost as they do not comprehensively capture the costs associated with the surgical procedures and associated complications. Based on Surrey et al. 2017, 36-46% of patients experienced complications associated with laparoscopy or hysterectomy surgeries.10 The increased healthcare resource utilization has been observed up to one year after the surgical procedure due to the complications.10 • For the surgery costs, AbbVie suggests using data on file from Soliman et al. 2017, who evaluated the 3- to 12-month healthcare expenditures following different surgical procedures among endometriosis patients using US insurance claims data.18 Total healthcare expenditures in 2014 USD over the 3-month period following the surgical procedure were estimated to be $10,625 ($10,428 paid by the plan) for laparoscopy and $14,590 ($14,411 paid by the plan) for hysterectomy.19 These 3-month costs on file are provided for ICER to use in their model with a 3-month cycle length.	Thank you for providing updated estimates. We've updated the surgery costs listed in Soliman et al. 2017 ($10,428 for laparoscopy and $14,411 for hysterectomy both in 2014 US costs) and inflated those costs to 2018 US dollars.

11.	Costs of productivity loss may be underestimated • Per Table 4.6, ICER derives the costs of productivity loss for patients with moderate to severe symptoms as average hourly wage multiplied by the total absenteeism hours reported for the overall endometriosis population in Soliman et al. 2017.20 AbbVie believes this approach underestimates the costs of productivity loss and suggests the following modifications. o First, productivity loss should include both absenteeism and presenteeism. Results from Soliman et al. 201720, Diamond et al. 201821, and Nnoaham et al. 201122 suggest that presenteeism is the major component of productivity loss in the workplace for patients suffering from endometriosis. o Second, productivity impacts should be estimated using total compensation (i.e. wages plus benefits). This would follow the best practices for calculating productivity impacts into CE analyses.23 Based on the US Bureau of Labor Statistics, the total employer cost averaged $35.87 per hour worked, which includes $24.49 for wages and salaries and $11.38 for benefits.24 o Third, the ICER model uses 13.2 hours lost due to productivity per 3-month period. This estimate was calculated by multiplying the weekly average absenteeism loss across all patients (1.1 hours) from Soliman et al. 2017 by 12.20 However, the 1.1 hours was for all patients, including those with mild symptoms. A more relevant estimate of weekly productivity hours lost for patients with moderate to severe pain could be obtained from the weekly estimated productivity loss at baseline from the elagolix Phase III trials.21 The results from the ISPOR 2018 poster suggest that patients with moderate to severe symptoms lost about 2.5-3.4 hours and 11.6-14.8 hours due to absenteeism and presenteeism, respectively. o Fourth, the ICER model allocates productivity costs to the proportion of women in moderate-to-severe pain health states and not to those in the reduced pain states. This is not consistent with the findings of Soliman et al. 2017, where even women with mild endometriosis symptoms reported positive hours of lost employment (1.9	We addressed these comments by including a modified societal perspective as a scenario analysis that includes both absenteeism and presenteeism. However, we did not include benefits in the lost productivity calculation. The fourth recommendation of the Second Panel on Cost-Effectiveness in Health and Medicine lists wages only as the opportunity cost of missed work. Our approach reflects this recommendation. Lost productivity is a function of the productivity of a member of society/employed individual. Productivity is best measured by a person's wage alone (not including benefits) as noted by the Second Panel's recommendation. Benefits are subject to additional factors outside of valuing an employee's productivity. Furthermore, encompassed in a workers benefit package is paid time off including sick time and vacation time. Applying wages plus benefits may inflate lost productivity by double counting the opportunity cost of missed work. Within recommendation 4, the Second Panel does acknowledge a lack of agreed upon methods for valuing broader societal effects and suggests analysts list all elements included in the analysis in the impact inventory table. For example, we did include additional hours for both absenteeism and presenteeism based on values estimated in Appendix B of Soliman et al. 2017. Specifically, we calculated the difference in lost productivity between women with 2 symptoms of endometriosis (7.8*4 weeks*3 month cycle) less the lost productivity of women with 0 symptoms (2.2*4 weeks*3 month cycle). This difference equated to approximately 67 hours of missed work per cycle.

	hours/week total) and household productivity (2.5 hours/week total).20 o Finally, costs of household productivity loss should also be included in the total costs of productivity loss. Data supporting these costs are also available from Soliman et al. 2017.20	
12.	The disutility parameters associated with laparoscopy and hysterectomy in the model are -0.06 and -0.07, respectively. These values were obtained from Ganz, et al. which in turn derived them from Roberts et al. However, the process by which these values were derived is not clear. **These values conflict with prior studies, which have found the disutility of hysterectomy to be substantially larger than -0.07. Additionally, it is unclear that the disutility values associated with laparoscopy and hysterectomy are essentially equal when one procedure is significantly more invasive than the other.**	Our model included a larger disutility for patient undergoing a hysterectomy than those receiving a laparoscopy. This issue raised is one of the magnitude of the difference. We believe that the estimates used are a reasonable approximation and have not found better evidence to suggest a larger difference. Of note, the nature of hysterectomies has changed over time. More are being done laparoscopically, so while the procedure itself is different, the laparoscopic nature is increasingly similar. Laparoscopic procedures are now the most common way to perform a hysterectomy.
13.	**Risk of fracture may be overestimated**. Per Table F4, ICER uses a relative risk of fracture for women of 1.5 per one standard deviation decrease of Z-score in BMD based on Kanis et al. 2001.29 The baseline osteoporotic fracture risk used by ICER was derived from Looker et al. 2017 among women aged 40-49 years. AbbVie disagrees with the approach used by ICER because both references predominantly focused on older women in the postmenopausal age range, while the target population is much younger (median age 32 years)**.** In addition, elagolix is not associated with a sustained reduction in BMD after treatment discontinuation. In the long-term extension studies EM-III and EM-IV, lumbar spine, hip, and femoral neck BMD Z-scores progressively moved towards baseline values during the post-treatment follow-up period. **AbbVie suggests that ICER remove fracture risk as a long-term AE in the evaluation.**	Fracture risk was not incorporated into the model until women reached the age of 40, therefore no fracture risk was estimated for women between the ages of 32-39. Moreover, for the average patient, incremental fractures were less than 1 for over 1,000 women over an 18 year time horizon, amounting to minimal changes in costs. The risk of fracture estimated for use in the cost-effectiveness models is quite low and based upon best available evidence. An abstract from Archer et al providing data from the phase III extension trials concludes, "In women with endometriosis-associated pain, long term elagolix treatment was associated with a decrease in lumbar spine BMD, which was greater with 200mg BID." Though bone density improves after discontinuing elagolix, a poster by Archer et al states, "In Elaris EM-IV, 50% of the women at 150 mg QD (34% at 200 mg BID) who had a decrease in lumbar spine BMD after 12 months of treatment had at least a 50% improvement off study drug in lumbar spine BMD at post-treatment month 6 (36% at 150 mg QD and 32% at 200mg BID for total hip; 32% at 150 mg QD and 35% at 200mg BID for femoral neck)." This implies that many women did not return to their baseline BMDs even 1 year after stopping therapy.
14.	Prior critiques of the ICER approach have found that adhering to a product-level spending cap requires that approximately one-third of new	We have repeatedly stated that ICER's budget impact analysis does not generate a "spending cap", but a signal to insurers and policymakers that

	drug spending be reallocated to other goods and services that could potentially be less cost-effective due to significant barriers to information. **In the case of elagolix, which ICER finds to be cost-effective, this could produce tremendous inefficiency.**	patient access might be threatened if new spending on any single product exceeds the general rate of growth in the U.S. economy – in fact, this signal might indicate that spending might need to be reduced for other services that are cost-effective in order to pay for a new intervention. Our analysis is intended to flag when special accommodations (e.g., outcomes-based contracting) might need to be made to make headroom in health care budgets for new innovations, full stop.
15.	A BI threshold approach punishes treatments of highly prevalent diseases like endometriosis, and therapies that meet a high unmet need like elagolix.	Our threshold is set only so that policy makers who wish to be alerted when percentage growth of health care resources used allocated to a health technology is growing faster than the growth of the national economy. Please refer to our value assessment framework https://icer-review.org/final-vaf-2017-2019/ for more details on this.
16.	For many women, as recognized by ICER on page 62 of the evidence draft report: "Elagolix is most likely to be considered as an alternative to GnRH agonists. The most commonly used GnRH agonist, leuprorelin acetate, is given by monthly injection." **However, treatment substitution effects were not accounted for in ICER's model, despite that they would affect the payer's pharmaceutical budget. This contradicts the review of treatment options and clinical guidelines conducted by ICER (Section 2.2, page 11).** Excluding substitutes unrealistically penalizes elagolix in the BI threshold approach, since the underlying assumption that all patients would otherwise have received watchful waiting is not supported by real-world claims data.	Our budget impact model derives cost inputs from the cost-effectiveness model for which efficacy estimates for both intervention and comparator were sourced from trial data. Since the trials compared elagolix to placebo based on the 200mg dose which was the source of efficacy estimates in our cost-effectiveness model, we used the same comparator (standard of care - rescue-pain medication) in our budget impact analysis. Please note that the budget impact includes not only elagolix/standard of care costs, but also costs associated with other health care resources utilized, including add-back hormonal therapy, depending on probability of use within the five year time horizon of the budget impact model.
17.	ICER BI calculation excludes cost offsets outside of the pharmacy budget from its analysis; this penalizes therapies that reduce medical costs (e.g., surgeries and hospitalizations) but not pharmacy benefit**. ICER's elagolix CE model shows elagolix cost offsets related to fewer surgeries (Tables 4.7 and 4.8), however, this cost offset is not factored into the BI threshold calculation.** If payers had a product level spending cap, it should consider cost offsets related to reduced surgeries calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care event as stated on page 66 of the evidence draft report.	We have revised our language on this in section 7 of the report. Our budget impact model derives cost inputs from the cost-effectiveness model, from year 1-5. These costs include both drug and non-drug costs, and would also include any cost offsets from reduced surgeries within this timeframe.

18.	**ICER evidence draft report does not present some of the information provided in ICER's analytic plan.** The missing information include the number of outpatient visits, the cardiovascular disutility, and information on the rescue pain agents (e.g., drug, dosage, utilization, and cost). AbbVie suggests that ICER provides detailed information on the model inputs used in their CE and BI models.	Detailed information on model inputs pertaining to drug dose and costs, health care resources used and associated costs, and utility/disutility estimates have been presented in the main report and appendix of our draft evidence report and will also be presented in our final evidence report.
19.	ICER's CE model assesses elagolix effects over an 18-year horizon, while BI is focused on a much shorter time horizon. The theoretical basis for these different time horizons in CE and BI models is unclear.	Budget impact models are designed to estimate the short-term budget impact and affordability of health technologies, while cost-effectiveness models are meant to represent the long-term cost and outcomes of a health technology, thus aiding health system-level decision making. Besides, cost-effectiveness models have time-horizons that are disease-specific. It is with this theoretical basis that our budget impact and cost-effectiveness models have differing time horizons.
20.	**There appears to be an inconsistency in the report regarding the threshold price analysis present within Table 4.16.** First, ICER assumes the price to be $7,000 per year ($583 per month) and calculates that the cost per QALY for NMPP (short run) at this price is $146,779. ICER then states that the price would need to be $578 per month to match the $150K per QALY threshold. If the price is lowered, cost per QALY should go down, not up, contradicting the threshold analysis results. **AbbVie recommends a careful review of the calculations which led to these results.**	Thank you for catching this typo. We have corrected the value-based prices in the report.
21.	P23-24, "In EM-I, 150 mgs daily dose elagolix provided a 14% difference from placebo in clinical response on [NMPP] (97.5% CI, 18 to 35) at three months and 11% (97.5% CI, 10 to 28) at six months." **Current values**: (97.5% CI, 5 to 35) and (97.5% CI, 10 to 28). **Corrected values**: (97.5% CI, 5 to 23) and (97.5% CI, 2 to 20); Taylor et al. 2017, Figure 1.	This has been corrected.
22.	Table 3.5 Placebo of Lilac PETAL. **Please consider both placebo arms in the trial: Placebo/Elagolix 150mg and Placebo/Elagolix 250mg; Diamond et al. 2014.**	We presented placebo results prior to crossover, during which time both placebo arms were combined. We followed the same approach with the Tulip PETAL trial from Acs 2015.
23.	Table 3.8 VAS score, DMPA-SC, week 24. **Current value:** -22.8. **Corrected value:** -17; Carr et al. 2014, Supplemental Figure 2.	This has been corrected.
24.	Table 3.8 VAS score, Elagolix 75 BID, week 24. **Current value**: -26.8. **Corrected value:** -23.6; Carr et al. 2014, Supplemental Figure 2.	This has been corrected.

25.	Table 3.9 Leuprorelin Acetate column. **Wrong source was referenced. The right source should be FDA prescribing information 2018.**	We have changed the reference to the 2018 updated prescribing information
26.	Appendix E. Diamond 2014, Percent days with prescription analgesic use. **Current value**: -2.4. **Correct value**: -2.6; Diamond et al. 2014, p. 366.	This has been corrected.
27.	Appendix E, Acs N. 2014, NMPP (digitalized) Mean Change (SE). **Current value:** 6 months. **Correct value:** 3 months; Ács et al. 2014, Figure 1.	This has been corrected.
28.	***Patient Organizations***	
29.	Terry Wilcox, Co-Founder & Executive Director, Patients Rising Now	
30.	First, the draft report recognized that "elagolix is taken daily as an oral formulation. This is likely to be viewed favorably by patients, as it may reduce healthcare complexity for women compared to GnRH agonists that are delivered via nasal spray or in-office intramuscular injections, or who are considering the potential for complications and time to recover from surgery." And the draft report goes on to further state that "in contrast to GnRH agonists, elagolix does not produce the "flare" or surge in hormones that leuprorelin acetate causes in the first few weeks of treatment. The flare can often lead to increased menstrual bleeding and other side effects that some women described as being uncomfortable." The fact that ICER recognizes those aspects of endometriosis and the potential qualitative benefits of elagolix is additionally distressing since the draft report also finds that women with endometriosis have noted their "…perception that health care providers are not taking their complaints seriously." **We point this out because, as discussed below, it also seems that ICER is not taking the real life implications of endometriosis for women with this condition – and their families – seriously enough.**	We do not believe that these two statements are mutually exclusive. The potential benefits of an orally available GnRH antagonist with properties similar to intramuscular or intranasal GnRH agonists is not intended to negate perceptions by women about how health care providers address symptoms of endometriosis. We also believe that the statement about elagolix is intended to imply that patients or doctors may have different perceptions about how endometriosis is evaluated or treated. We also note that in the report, section 1.4, we highlight a broad range of concerns that were discussed with women with endometriosis and patient advocates.
31.	While the specific anatomical pathology of endometriosis is relatively straight-forward (i.e., the presence of endometrial tissue at locations other than the uterus), the reproductive hormonal/endocrine system for a premenopausal woman is very complex. As one review article described it, "Given the complex nature and likely multifactorial	We agree that there are many different treatments used for symptomatic women with endometriosis. These include both FDA approved and unapproved therapies. The ICER review focused on comparative studies with elagolix. The review explicitly focused on non-

	etiology of endometriosis pathogenesis, a vast number of pharmacologic target options exist. Strategies for medical intervention include drugs that suppress ovulation and/or induce a hypoestrogenic state, medications that act directly on endometriotic deposits, anti-inflammatory agents, and immunomodulators." **We also note that this article discusses several additional treatment options not discussed in ICER's draft report, and we concur with its conclusion that FDA-approved and ''off-label'' treatments for endometriosis, "are complementary to each other in the individualized care for this complex and challenging disease."**	surgical interventions, specifically focusing on hormonal treatments including hormonal contraceptives, GnRH agonists and aromatase inhibitors.
32.	The complexity of treating endometriosis was also highlighted in a review of clinical guidelines published in November 2017 (which ICER did not appear to include in its analysis) that found only 10 of 152 recommendations were common across the seven guidelines assessed. **We also found striking that the authors of this review explicitly stated in their publication that they "involved a woman with endometriosis in the design and delivery of our research," something that ICER apparently did not do.**	Thank you for your comments. As is standard practice, ICER works closely with patients throughout the entire review process. This begins very early, during our scoping phase when we reach out to hear from patients and patient groups. We ask a patient to review our draft report document; and welcome public comments from throughout the patient community on several occasions throughout the 8-month review. At our July public meeting, we will have two active patients participating throughout the day to lend their perspective on the disease and its treatment.
33.	Our first concern about the draft report's cost effectiveness analyses is the information about lost productivity. For example, the data included in Table 4.6 on page 50 are perhaps the minimum figures that could be derived from the available sources and excluding the full scope of productivity cost data related to endometriosis leads to skewed and biased conclusions in the draft report. Specifically: • The "Average Hourly Wage" in Table 4.6 only represents actual wages to individuals. However, this section is titled "Societal Perspective Inputs" – and the Bureau of Labor Statistics (BLS) data on total compensation is what other researchers have used for their productivity calculations. Therefore, we believe ICER should also use that data point since it more accurately reflects the total marginal cost to an employer for each employee. And for December 2017, BLS	Please refer to the response above in Row 11.

	reported that amount to be $35.87/hour, rather than the $24.34/hour wage number ICER chose to use. • In the second row of Table 4.6, while ICER lists 13.2 hours lost/3 months, that number is inconsistent with (and much lower than), what has been reported elsewhere. Specifically, the 2017 article by Soliman et al., which compared women with endometriosis to controls, calculated that women with endometriosis lost per week 1.1 hours of employment productivity from absenteeism and 5.3 hours from presenteeism – and an additional 4.8 hours in household productivity. Thus, using Soliman's data, lost workplace productivity in Figure 4.6 would be 83.2 hours for every three months, and a total lost productivity of $11,937.54 per year. In addition, an even higher figure could be discussed for the lost work productivity from endometriosis since we assume the $15,000/year amount cited on page 1 of the draft report is from the 2011 prospective study by Nnoaham et al. of women scheduled for laparoscopy, which reported lost productivity in the USA from endometriosis of $15,737/year in 2007 dollars – and thus the equivalent 2018 amount would be significantly higher. Therefore, we urge ICER to recalculate its Societal Perspectives analysis using total compensation (rather than only wages), and update lost time figures to reflect – at a minimum – both workplace presenteeism and absenteeism. We believe more accurate data inputs would demonstrate Soliman's conclusions that "In comparison with other conditions, women with endometriosis have reported greater work productivity and activity impairment than patients with conditions such as rheumatoid arthritis. Furthermore, the absenteeism rates reported in this study are higher than those reported for other pain conditions such as headaches and back pain."	
34.	Second, we concur with ICER's finding that the "short duration of therapy with elagolix versus placebo or other active comparators means it is difficult to extrapolate the benefits and risks of long-term use. Available comparative data assessed elagolix versus placebo at three or six months." Similarly, we concur with ICER evidence rating for	We appreciate the concerns raised that our evidence reviews, and modeling findings may be perceived as contradictory. We do not believe this is the case and will further revise our final report and executive summary to highlight this important concern. A P/I rating may be

	Elagolix of "Promising but Inconclusive" – given that it is the first medicine with this mechanism of action and has yet to be approved by the FDA, that finding is far from surprising. **However, this degree of uncertainty also leads to significant uncertainty in the draft report's conclusions.** For example, we observed that because of the small incremental QALY's in ICERs calculations any changes to that finding – such as slight modifications to the calculated social impact (e.g. productivity) – results in large difference in incremental QALYs. This is also illustrated in the Sensitivity Tornado analyses in Figures 4.2, 4.3, 7.1 and 7.2. **We also believe that the uncertainty illustrated by the sensitivity analysis should be highlighted in the body of the report rather than relegated to the end. This would better reflect the perspectives of women with endometriosis where there is so much individual variability and uncertainty about their clinical situation and options.**	associated with a cost effectiveness analysis that shows the drug to be cost effective or not. It is true that an evidence rating that shows net harm or lack of benefit would not be expected to be a cost-effective drug. Rather, the evidence rating acknowledges that considerable data exists supporting the safety and efficacy of elagolix for women with moderate to severe symptoms of endometriosis. However, given that elagolix does not offer a cure and that stopping the medicine results in a return of symptoms, this drug may be used for prolonged periods of time in women who have a response. It is this long-term use as well as the potential for long-term side effects not captured in published studies to date that lead to our promising but inconclusive rating. The modeling findings are derived from evidence to date and quantify the cost effectiveness given the likely cost of the drug and the downstream benefits and side effects.
35.	And third, by evaluating a medicine before it has been approved by the FDA means that not only is the manufacturer's list price unknown, but the label indications and warnings are also unknown. We recognize that to determine a "placeholder" for price, ICER uses the "projected price" from Seeking Alpha a "financial market research firm," which is a free and publicly available news source. However, there are many other proprietary market research firms in the competitive business of projecting prices and other financial aspects of potential therapies before FDA approval. **Has ICER consulted any of those analyses before picking the publicly available free option?**	We agree there are many other options for projected prices beyond Seeking Alpha. However, a publicly available estimate does not make the projected price invalid. Furthermore, we estimate value-based prices from our threshold analyses to further inform the discussion.
36.	We raise these points because ICER's "health system" and "third party payer" perspectives, puts ICER into the role of purchaser – or advisor to purchasers and payers – rather than value analyst. **In other words, ICER seems to be declaring that if the launch price is above what ICER determines as "just" then the company and its product should be shunned – irregardless of the clinical benefit the therapy would bring to patients, and ignoring the very diverse set of patient populations and payers in the US and their range of value considerations based**	We respectfully disagree with this point. This ICER review sought to evaluate: 1) the published comparative evidence supporting the use of elagolix in women with moderate to severe symptoms of endometriosis, 2) evaluate the cost-effectiveness of elagolix from a health systems perspective, and 3) seek input from patients, clinicians, researchers, industry and payers to identify other key issues that go beyond the evidence and cost-effectiveness. We include each of these three pieces

	upon their structure, governance, and enrollee population – an inherent complexity of the U.S. health care financing system that ICER's draft report doesn't address.	and publicly present them at a meeting where our advisory council provides recommendations.
37.	Reference #37 has an incorrect link to NICE document. The correct link is https://www.nice.org.uk/guidance/ng73#	Thank you. We have corrected this link in our revised report.
38.	On page 43, the draft report indicates that Excel is from "Redmond, VA". We suspect that it is a proofreading error, and that it should be "Redmond, WA" which is where Microsoft, the producer of Excel as part of the Microsoft Office Suite is headquartered. **An additional aspect of this that would be helpful for ICER to clarify is what version of Excel was used to run the model as well as what computer system and CPU were used. Given that there have been problems with both the use of Excel for computational models (e.g., Harvard Economics Professors misusing Excel published erroneous analyses and conclusions), and computer CPUs that produced incorrect calculation, we think ICER should include those technical specifications in its reports similar to how biomedical researchers describe their research methodologies by including the type and model of key instruments used in their experiments.**	Thank you for catching this typo. We've corrected the typo to "Redmond, WA." To address your comment on calculation errors, we follow good research practices for model validation outlined by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Specifically, we perform internal model validation exercises that vary all inputs to extreme values to identify errors in any calculations. We also compare our results to previously published modeling analyses. Please see Section 4 in the report for further details on model validation procedures as well as estimate comparisons to other models.
39.	On page 3 of the draft report it is stated that "Though no studies have been performed using add-back therapy for elagolix, it may be expected that such therapy would be considered for long-term use of higher doses of elagolix that result in full ovarian suppression." However, later in the report it notes that studies of elagolix with add-back therapy are ongoing for patients with endometriosis, as well as for women with uterine fibroids and heavy menstrual bleeding – and this information is also available at ClinicalTrials.gov. **Therefore, the sentence on page 3 should be edited to clarify the existence of the ongoing research.**	The statement on page 3 of the report has been clarified to state that there have been no "published" studies reporting on the use of add-back therapy with elagolix.
40.	The draft report's cost-effectiveness analyses are presented separately for two different clinical indications – including threshold price calculations in Table 4.15 and 4.16 on page 56. However, this implies that there exists a platform for indication specific pricing, which doesn't	Please refer to the response above in Row 6.

	exist in the US – at least not for connected conditions such as dysmenorrhea and non-menstrual pelvic pain. **We would appreciate it if ICER clarified its thinking behind – or the utility for – the draft report's bifurcated analysis and section of the report.**	
41.	Patients Rising Now believes that ICER's draft report does not reflect the quality of life, productivity, and complexity of diagnosis and treatments that women with endometriosis actually face. Without adequately incorporating patients' voices into the process of defining and assessing the value of their treatment options, ICER's draft report creates a warped view of a complex situation, and may perpetuate biases and inequities in diagnosis, treatment, regulations, payment, and R&D efforts. **We recommend that ICER more fully address the range of real-world costs endometriosis has for women and their families – particularly the costs of personal and workplace productivity. We also recommend that ICER continue to assess and examine its methodology and perspectives for its work.**	We always strive to estimate the real-world costs of the conditions we evaluate in our reports. In this case, we sought to properly include relevant information regarding the societal perspective that could be adequately modeled. With regard to the specific comment on productivity, we note that our modified societal analysis is focused specifically on the effects of absenteeism and presenteeism.
42.	Amy M. Miller, PhD, President and Chief Executive Officer, Society for Women's Health Research	
43.	**SWHR urges ICER to delay finalizing the Draft Evidence Report (DER) until new therapies, such as elagolix, are FDA-approved and more published data is available to model the comparative clinical and economic value of new treatment options for endometriosis.** [A]fter reviewing the DER, SWHR is concerned that the current timing of ICER's value assessment of elagolix may be premature. Throughout the DER, ICER repeatedly acknowledges important limitations both in the available evidence and in its own analysis that call into question the timing of this value assessment and the validity of the conclusions. The following quotes demonstrate the multiple limitations of ICER's endometriosis DER analysis: • Page 43: "Importantly, we note that, due to differences in trial design, outcome measurement, the age of comparator studies, and other factors as highlighted in Section 3, our only recourse was to model the cost-effectiveness of elagolix as compared to no active treatment (i.e., placebo)." • Page 57: "We searched the literature to identify models that were	We agree with this statement that there are limitations in the available evidence and the cost-effectiveness modeling required a number of important assumptions. However, we also believe that elagolix, if approved by the FDA, will be available for use by patients and clinicians, and payers will be asked to make decisions in the short term. Reliable information will be needed, and this report uses data that is currently available and highlights the limitations of this data as well as the qualitative input of a range of key stakeholders. The issues raised here are common for newly approved therapies, but delaying the release of available information leaves patients, clinicians and payers in the position of having to make important decisions without access to unbiased information such as that provided in this report.

	similar to our analysis, with comparable populations, settings, perspective, and treatments. We found no published economic evaluations of elagolix in women with moderate-to-severe endometriosis related pain." • Page 59: "We note, however, that the only comparison available because of data limitations was to no active medical management (i.e., placebo), which is an unrealistic clinical strategy in women with moderate-to-severe endometriosis-associated pain." • Page 59: "There were several important and distinctive limitations to our analysis… severe limitations in available data precluded any comparison to another active treatment such as GnRH agonists and oral contraceptives. It is therefore likely that clinical benefits in our analysis are overstated to some extent, although the magnitude of this effect is unknown without comparable data. We also modeled cost-effectiveness using an assumed annual price, as the drug is not yet FDA-approved and the actual price is unknown." Therefore, as we stated at the outset, SWHR urges ICER to delay finalizing the DER until new therapies, such as elagolix, are FDA-approved and more published data is available to model the comparative clinical and economic value of new treatment options for endometriosis. If ICER insists on moving forward with this DER, we strongly encourage ICER to take immediate steps to strengthen its analysis by making needed refinements to its methodology, modeling techniques, and key inputs.	
44.	**1) ICER should account for lost productivity in the cost-effectiveness base case, instead of using lost productivity to estimate cost-outcomes from a modified societal perspective as a scenario analysis. Further, ICER's data capture of lost productivity must account for both presenteeism and absenteeism.** Characterized by pain symptoms, endometriosis has a negative effect on productivity. Women with endometriosis suffered a 38% loss of work and productivity because of the symptoms. Total productivity loss	Please refer to the response above in Row 11.

	in employed women with endometriosis averages 6.3 hours per week, with the majority of that loss due to presenteeism. Endometriosis also severely affects household productivity, with an average of 4.9 hours per week lost. Both lost work and household productivity can vary as a function of symptom severity, with patients who experience moderate to severe symptoms reporting the highest lost productivity. On average, 6.6 days per annum are lost because of absenteeism and 31.8 days per annum are unproductive days at work, resulting in a total loss (absenteeism and presenteeism) of about $10,178 per year. Applying the most commonly reported prevalence of endometriosis (10%) to the number of the employed U.S. female population aged 18-49 in 2014 (44,614,000), the total loss (absenteeism and presenteeism) would be about $45.4 billion annually.	
45.	**2) Endometriosis quality of life data used in ICER's analysis may not adequately capture the disproportionate effect this disease has on women, their families, and society as a whole.** Endometriosis greatly affects the quality of life for women, including their relationships and their ability to perform. Endometriosis often negatively impacts sexual relations, productivity in the workplace and at home, appetite, exercise, emotional well-being, sleep, and relationships. The Endometriosis Health Profile-30 questionnaire (EHP-30) and its shortened version (EHP-5) are the only endometriosis-specific tools for collecting patient-reported outcomes on quality of life that were designed with input from patients. While these tools capture the physical, emotional, and social impact of endometriosis on the patient, they do not adequately capture the burden of endometriosis on the family. In addition, the EHP-30 has not been widely adopted into clinical practice.	Chronic conditions associated with pain, like endometriosis, often cause damage far beyond what is captured in pain scores. However, in order to calculate a preference score that can be used to calculate quality-adjusted life years (QALYs), the recommended and standardized metric for comparing effectiveness of interventions across disease states, we relied on the numeric pain rating scale. Without directly elicited EQ-5D scores from trial evidence and no mapping function between EHP-30 or EHP-5 QoL instruments that were used in the trials and the EQ-5D, we mapped EQ-5D scores from the numeric pain rating scale and the EQ-5D. We varied the mapped EQ-5D score and found it had one of the largest impacts on the model findings. Furthermore, in our summary and comment section within the comparative value chapter, we've noted lack of available quality of life data as a limitation. Specifically, "Further evidence on active comparators and directly elicited health utility scores from elagolix Phase III trial-evidence could validate or refute the model findings."
46.	**ICER should not rely solely on the wholesale acquisition cost (WAC) of a drug (whose actual price is not yet known) to estimate a new**	We typically estimate budget impact based on the WAC, the estimated net price, and the prices that would achieve cost-effectiveness

	treatment's budget impact. ICER relies on the wholesale acquisition cost of a drug to estimate the budget impact of a new treatment (and therefore the estimated number of patients who can access the treatment). Not taking into account the rebates and discounts frequently negotiated between payers and pharmaceutical manufacturers is likely to lead to inaccurate budget impact estimations. Similarly, basing the DER on a placeholder WAC estimate is likely to result in incorrect estimates of the value of new treatments. If payers rely on flawed estimates, it could have significant implications for women's access to important treatments for endometriosis. **We encourage ICER to consider accounting for likely rebates and discounts in its estimates.**	thresholds between $50,000 and $150,000 per QALY, so that policymakers can view the results at multiple possible price points. In this case, the comment is untrue -- we do not yet have a published price for elagolix, and so did not include WAC; we were limited to the projected price as well as our threshold estimates to estimate potential budget impact.
47.	**ICER should develop novel approaches to assessing value.** Cost-effectiveness analysis (CEA) based on quality-adjusted life years (QALY) may not adequately capture the differences in preferences and clinical characteristics of women with endometriosis. While we recognize that ICER has committed to using CEA as the basis for its value framework, many stakeholders have acknowledged the limitations of QALY-based CEA, particularly in accounting for heterogeneity. Women with endometriosis vary in age, employment, caregiver status, and socioeconomic status. A simple cost-effectiveness ratio cannot capture those differences. If the QALY is used (despite the limitations noted above), it should be recognized that no single threshold can or should be universally applicable, as thresholds are likely to vary by decision-maker, population, and disease.	While we agree that CEA and QALYs may not capture the entirety of differences in preferences and clinical characteristics of women with endometriosis, QALYs are the recommended metric of effectiveness for comparisons across interventions. Further, as noted in a recent commentary by Neumann and Cohen, "individuals who dislike QALYs tend not to offer solutions beyond nebulous comments about the need to place patients at the forefront of decisions,"[1] further noting that avoidance of QALYs does not obviate the need to confront the tradeoffs necessary in healthcare decision-making, it simply masks them. CEA by definition is an aid to decision making and can never fully replace the judgement of clinicians and patients when making decisions about treatment choice. We acknowledge there is no single threshold, which is why ICER presents value-based prices across multiple thresholds of cost-effectiveness.

[1] Neumann PJ, Cohen JT. QALYs in 2018: Advantages and concerns. JAMA 2018; doi:10.1001/jama.2018.6072 (published online).

48.	5) ICER should refine its new transparency pilot program before expanding its use beyond migraine prevention and endometriosis reviews. SWHR commends ICER for its commitment to a transparent public engagement process to ensure that all stakeholders have the opportunity to provide input to its reports. We are encouraged by a new pilot program ICER recently announced to make available draft executable economic models during the assessment review process, which represents an important next step in ICER's stakeholder engagement efforts. SWHR agrees with ICER that enabling the direct viewing of a model's structure, estimates, key assumptions, and calculations may allow for valuable feedback during the public comment period that follows the release of an ICER DER. Consistent with ICER's intended goal to "provide the opportunity for manufacturers, and ultimately patient groups and other qualified stakeholders to gain even greater insights into draft models so that their feedback can enhance the accuracy and relevance of final versions," we urge ICER to: 1) expand model access beyond manufacturers to qualified researchers, 2) eliminate financial barriers to access by waiving payable fees to ICER's academic collaborators, and 3) share models that qualified researchers can alter for their own analytic purposes.	Thank you for your comments on our transparency commitments. We are currently integrating feedback from the participants in our pilot efforts to better ascertain how to refine our processes moving forward. Regarding your comments, we are unclear what is meant by the term "qualified researchers". One of the stated concerns with the idea of fully open-source modeling is protection of academic intellectual property; given that the purpose of our transparency efforts is to provide an opportunity for model validation and review among those with a stake in the topic at hand, we do not believe that opening this process up to any researcher with a passing interest would serve any useful purpose as part of this process. Furthermore, our pilot efforts allowed for manufacturer participants to include any researchers consulting with them on the project, as long as they agreed to be named and to be subject to the confidentiality provisions that were in place. Regarding financial barriers, the additional work required of our academic collaborators to be part of this effort is significant and requires compensation. Manufacturers gave us input that the proposed fees were acceptable, and any expansion of our efforts to patient groups would not involve a fee. Regarding the point on model-sharing, we are unclear whether this is describing the current approach or some future "open-source" setting. While we are part of multi-stakeholder efforts to discuss open-source ideas, the evolution of those ideas is at a very early stage, as no consensus has been reached on releasing academic IP into the public domain.