Primary Efficacy and Safety Results from Two Double-blind, Randomized, Placebo-controlled Studies of Elagolix, an Oral Gonadotropin-releasing Hormone Antagonist, in Women with Endometriosis-associated Pain

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Disclosures

Sukhbir S. Singh was a primary investigator in therapeutic trials for endometriosis and fibroids sponsored by Allergan, AbbVie, Bayer; served as a speaker and advisor for Allergan, AbbVie, Bayer, Hologic and Cooper Surgical. Hugh S. Taylor has received research support from OvaScience and Pfizer and has served as a consultant for AbbVie, Pfizer, Bayer, Observa, and OvaScience. Linda Giudice has received research support from Bayer Healthcare LLC, serves on advisory boards for AbbVie Inc, Juniper Pharmaceuticals, NextGen Jane, Myovant Pharmaceuticals, and is a past President of the World Endometriosis Society and President-elect of the International Federation of Fertility Societies. Bruce Lessey was a study investigator and received research support from AbbVie and Pfizer. Scientific advisor for CiceroDx. Mauricio S. Abrao has received research support from FAPESP, has served as an advisor for AbbVie and BayerShering, and has served as Editor-in-Chief of the Journal of Endometriosis and Pelvic Pain Disorders. Jan Kotarski was a study investigator. W. Rachel Duan, Brittany Schwefel, James Thomas, and Kristof Chwalisz are AbbVie employees and hold stock or stock options.

AbbVie Inc. participated in the study design, research, analysis, data collection, interpretation of data, reviewing, and approval of the publication.

Acknowledgements

Jane Rodgers, PhD, and Amy M Spiegel, PhD, both of AbbVie, Inc., provided medical writing support for this presentation.
**Study Objectives**

To evaluate the efficacy and safety of elagolix compared to placebo in the management of moderate to severe endometriosis-associated pain.

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**Background**

Elagolix for the Treatment of Endometriosis-associated Pain

**Elagolix:**

- Is an oral, non-peptide, gonadotropin-releasing hormone ( GnRH ) antagonist
- Results in dose dependent suppression of gonadotropins and ovarian sex steroids
  - Hormone suppression is rapid and reversible
  - Partial estradiol suppression at 150mg QD
  - Nearly full estradiol suppression at 200mg BID

**Female Hypothalamic-Pituitary-Gonadal Axis**

- Hypothalamus
- Anterior Pituitary Gland
- Ovaries
- Estradiol Progesterone

GnRH

- GnRH antagonist

GnRH receptor

LH FSH

**Methods**

**Study Design:** Two, Double-blind, Randomized, Placebo-controlled Studies

- **Elaris Endometriosis I (EM-I)** was conducted in North America (NCT01620528)
- **Elaris Endometriosis II (EM-II)** was global (NCT01931670)

**Participants were:**
- premenopausal women (18-49 years)
- surgically diagnosed with endometriosis
- moderate/severe dysmenorrhea and non-menstrual pelvic pain

**Washout Period**
- of hormone therapies (if applicable)

**Screening Period**
- (Up to 75 days)

**Treatment Period**
- (6 months)

- **Elagolix 200 mg BID**
- **Elagolix 150 mg QD**
- **Placebo**

**Enter: Follow Up**
- (Up to 12 Months)
- Or
- **Extension Study**

**Menstrual Cycle 1**
- Day 1
- Randomization

**Menstrual Cycle 2**
- M1
- M2
- M3
- M4
- M5
- M6

**Safety assessments**

- Daily pain assessments in electronic diary
- Co-primary Efficacy Endpoints: Enter Follow Up or Extension Study

**Assessments**

**Endometriosis-associated Pain Assessments**
- Dysmenorrhea and non-menstrual pelvic pain (4-point scales): daily, electronic, endometriosis pain impact diary
  - **Co-primary efficacy endpoints:**
    - the proportion of responders (pain reduction and stable/decreased rescue analgesic use) at month 3 based on dysmenorrhea and non-menstrual pelvic pain scores

**Quality of Life Assessment**
- 30-item Endometriosis Health Profile (EHP-30) is a self-administered questionnaire:
  - 5 core dimensions assessing pain, control and powerlessness, emotional well being, social support, and self image; 1 modular questionnaire about sexual intercourse

**Safety**
- Adverse events
- Changes in bone mineral density
**Results**

**Patient Disposition**

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>Elagolix 150 mg QD</th>
<th>Elagolix 200 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>n=374</td>
<td>n=249</td>
<td>n=248</td>
</tr>
<tr>
<td>Completed</td>
<td>n=274</td>
<td>73.3%</td>
<td>78.7%</td>
</tr>
<tr>
<td>Study 2</td>
<td>n=360</td>
<td>n=226</td>
<td>n=229</td>
</tr>
<tr>
<td>Completed</td>
<td>n=196</td>
<td>73.8%</td>
<td>75.0%</td>
</tr>
<tr>
<td>Placebo EM-I</td>
<td>n=374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>n=274</td>
<td>73.3%</td>
<td></td>
</tr>
<tr>
<td>Placebo EM-II</td>
<td>n=360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>n=178</td>
<td>78.8%</td>
<td></td>
</tr>
</tbody>
</table>

*1 woman in Study 1 and 2 women in Study 2 were randomized but not treated.
QD = once daily; BID = twice daily

**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Elagolix</td>
</tr>
<tr>
<td></td>
<td>150 mg QD</td>
<td>200 mg BID</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>32 (6.4)</td>
<td>32 (6.0)</td>
</tr>
<tr>
<td>Race, % white, % black</td>
<td>86, 9</td>
<td>89, 8</td>
</tr>
<tr>
<td>BMI, kg/m², mean (SD)</td>
<td>28 (6.2)</td>
<td>28 (6.3)</td>
</tr>
<tr>
<td>Months since surgical diagnosis, mean (SD)</td>
<td>45 (30)</td>
<td>41 (29)</td>
</tr>
<tr>
<td>Dysmenorrhea, mean score (SD)*</td>
<td>2.2 (0.4)</td>
<td>2.2 (0.5)</td>
</tr>
<tr>
<td>Non-menstrual pelvic pain, mean score (SD)*</td>
<td>1.6 (0.5)</td>
<td>1.6 (0.5)</td>
</tr>
</tbody>
</table>

Baseline characteristics were well balanced between treatment groups & studies.

P<0.05 (*) indicated for heterogeneity among treatment groups based on one-way ANOVA testing.

a. Pain scale ranges from none (0) to severe (3) and was recorded in a daily electronic diary.

Table modified from Taylor et al. *N Engl J Med*. May 19, 2017
Results
Co-Primary Endpoints: Percentage of Responders at Month 3

Compared to placebo, each dose of elagolix led to a significantly greater responder rate for dysmenorrhea and non-menstrual pelvic pain at month 3.

Figure from Taylor et al. N Engl J Med. May 19, 2017

Results
Effects of Elagolix on Dysmenorrhea

Compared to placebo, each dose of elagolix led to significant improvements in dysmenorrhea at month 1, which were sustained through month 6.

The statistical significance vs. placebo is indicated for P<0.05 (*), P<0.01 (**), and P<0.001 (**). Figure from modified from Taylor et al. N Engl J Med. May 19, 2017
### Results

**Effects of Elagolix on Non-menstrual Pelvic Pain**

Compared to placebo, each dose of elagolix led to significant improvements in non-menstrual pelvic pain early on, through month 6.

The statistical significance vs. placebo is indicated for P<0.05 (*), P<0.01 (**), and P<0.001 (***)

Figure from modified from Taylor et al. N Engl J Med. May 19, 2017

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### Results

**Effects of Elagolix on Quality of Life**

Compared to placebo, elagolix 150 mg QD and 200 mg BID led to significant improvements in EHP-30 pain, control & powerlessness, and emotional well-being dimension scores at month 6.

The statistical significance vs. placebo is indicated for P<0.05 (*), P<0.01 (**), and P<0.001 (***)

Figure from modified from Taylor et al. N Engl J Med. May 19, 2017
Results
Effects of Elagolix on Quality of Life

Elaris EM-I: EHP-30 Dimension Scores
(results were similar for Elaris EM-II)

Compared to placebo, elagolix 200 mg BID led to significant improvements in EHP-30 social support, self-image, and sexual intercourse dimension scores at month 6.

The statistical significance vs. placebo is indicated for P<0.05 (*), P<0.01 (**), and P<0.001 (***)

Figure from modified from Taylor et al. N Engl J Med. May 19, 2017

Results
Summary of Safety: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Elaris EM-I</th>
<th></th>
<th>Elaris EM-II</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Elagolix 150 mg QD</td>
<td>Elagolix 200 mg BID</td>
<td>Placebo</td>
</tr>
<tr>
<td>N (%)</td>
<td>374</td>
<td>249</td>
<td>248</td>
<td>360</td>
</tr>
<tr>
<td>Any adverse event (AE)</td>
<td>277 (74%)</td>
<td>201 (81%)</td>
<td>205 (83%)**</td>
<td>260 (72%)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>12 (3.2%)</td>
<td>2 (0.8%)</td>
<td>7 (2.8%)</td>
<td>12 (3.3%)</td>
</tr>
<tr>
<td>Any severe AE</td>
<td>56 (15%)</td>
<td>26 (10%)</td>
<td>43 (17%)</td>
<td>32 (8.9%)</td>
</tr>
<tr>
<td>Any AE leading to discontinuation</td>
<td>22 (5.9%)</td>
<td>16 (6.4%)</td>
<td>23 (9.3%)</td>
<td>22 (6.1%)</td>
</tr>
</tbody>
</table>

AEs occurring ≥ 15% in at least 1 treatment group

<table>
<thead>
<tr>
<th></th>
<th>Elagolix 150 mg QD</th>
<th>Elagolix 200 mg BID</th>
<th>Elagolix 150 mg QD</th>
<th>Elagolix 200 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Flush</td>
<td>26 (7.0%)</td>
<td>59 (24%)***</td>
<td>37 (10%)</td>
<td>51 (23%)***</td>
</tr>
<tr>
<td>Headache</td>
<td>37 (9.9%)</td>
<td>38 (15%)</td>
<td>51 (14%)</td>
<td>42 (19%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>51 (14%)</td>
<td>25 (10%)</td>
<td>41 (11%)</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>Discontinuation due to hot flush</td>
<td>0</td>
<td>2 (0.8%)</td>
<td>0</td>
<td>2 (0.9%)</td>
</tr>
</tbody>
</table>

- The severity of hot flushes was mild in the majority (>50%) of women in each treatment group
- Discontinuation rate due to hot flushes was < 3% in elagolix groups
**Results**

Distribution of Z-scores at Baseline and Month 6: Lumbar Spine

Graphs represent median, min, max, Q1, and Q3 of the group Z-scores.


At month 6, all lumbar spine BMD Z-scores were above -2.0, within or above the normal age/race-matched range (ref)

**Results**

Categorical Representation of Mean Percent Change from Baseline to Month 6 for Lumbar Spine BMD

At month 6, the majority of women (>50%) in each treatment group had an increase, no change, or changes in BMD of <3%

Figure from modified from Taylor et al. N Engl J Med. May 19, 2017
**Summary**

In women with endometriosis-associated pain, 6 months of elagolix treatment (150 mg QD and 200 mg BID):

- Led to dose-dependent and clinically meaningful improvements in dysmenorrhea and non-menstrual pelvic pain compared to placebo.
  - The effects on dysmenorrhea occurred as early as month 1, and were maintained through month 6 of treatment.

- All lumbar spine BMD Z-scores were within the expected range for age following elagolix treatment.¹

- Showed a safety profile that included hypoestrogenic effects and was consistent with the mechanism of action.


**Strengths and Limitations**

**Strengths**

- Oral GnRH antagonist treatment option for patients
  - No risk of flare

- Patient inclusion based on pain symptoms

- Characteristics similar to other studies of CPP and endometriosis (Gylfason and Parazzini)

- Two dosing options offers individualized approach

- Pain results controlled for rescue analgesia use (narcotic and NSAIDS)
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- Oral GnRH antagonist treatment option for patients
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**Limitations**
- Pain is complex
  - Other comorbid conditions possibly causing NMPP (i.e. pelvic floor dysfunction, GI/GU conditions, adhesions)
- Patient inclusion not based on stage of disease
  - deep endometriosis versus superficial
  - large endometriomas were excluded
- Long-term therapy follow up required