Original Research

Health-Related Quality of Life Improvements in Patients With Endometriosis Treated With Elagolix

Hugh S. Taylor, MD, Ahmed M. Soliman, MS, PhD, Beverly Johns, PhD, Robin M. Pokrzywinski, PhD, Michael Snabes, MD, PhD, and Karin S. Coyne, PhD

OBJECTIVE: To evaluate the effects of elagolix on clinically meaningful improvements in health-related quality of life (HRQOL) measured by the EHP-30 (Endometriosis Health Profile-30).

METHODS: Data from two phase III trials of elagolix for moderate to severe pain associated with endometriosis were pooled and analyzed as three groups: placebo, elagolix 150 mg once daily, or elagolix 200 mg twice daily. Patients were administered the EHP-30 questionnaire at baseline, and at months 1, 3, and 6 of treatment. Previously established responder definitions were applied to determine percentages of patients with clinically meaningful EHP-30 improvements. The probability of meeting EHP-30 responder definitions with elagolix compared with placebo at months 3 and 6 was determined by Poisson regression analysis, controlling for baseline scores.

RESULTS: At month 6, the probabilities of meeting EHP-30 subscale responder definitions for pain, control and powerlessness, self-image, social support, emotional well-being, and sexual intercourse were 169% (adjusted relative risk [aRR]: 2.69, 95% CI 2.26–3.21), 129% (aRR 2.29, 95% CI 1.96–2.67), 80% (aRR 1.80, 95% CI 1.54–2.11), 70% (aRR 1.70, 95% CI 1.47–1.97), 67% (aRR 1.67, 95% CI 1.45–1.92), and 62% (aRR 1.62, 95% CI 1.36–1.92) greater, respectively (all $P<.001$), in the 200-mg group than in the placebo group. Although lower in magnitude than the 200-mg group, the 150-mg group also had greater probabilities of meeting responder definitions than the placebo group for all subscales except sexual intercourse. The probabilities of meeting responder definitions for pain, control and powerlessness, self-image, social support, and emotional well-being were 75% (aRR 1.75, 95% CI 1.44–2.14), 50% (aRR 1.50, 95% CI 1.25–1.80), 22% (aRR 1.22, 95% CI 1.01–1.47), 30% (aRR 1.30, 95% CI 1.09–1.53), and 35% (aRR 1.35, 95% CI 1.16–1.57) greater, respectively (all $P<.05$), in the 150-mg group than in the placebo group.

CONCLUSION: Patients with moderate to severe pain associated with endometriosis and were treated with elagolix experienced clinically meaningful HRQOL improvements.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov, NCT01620528 and NCT01931670.

FUNDING SOURCE: AbbVie Inc.

Endometriosis is a chronic gynecologic condition characterized by growth of endometrial tissue outside the uterus.[1] Pain symptoms are a central feature of endometriosis, along with infertility and chronic fatigue,[1,2] and current treatment guidelines prioritize pain management.[3,4] Endometriosis reduces women's health-related quality of life (HRQOL),[5] resulting in

impairments in physical functioning,[6–9] diminished social life, difficulties in intimate relationships,[6,7,10,11] and decreased productivity.[6–8,12]

Patient-reported outcome measures such as the EHP-30 (Endometriosis Health Profile-30)[13–15] are increasingly employed to evaluate therapeutic efficacy and guide clinical decision making.[16] In 2009, the U.S. Food and Drug Administration published guidance on using patient-reported outcome measures in clinical trials, emphasizing the establishment of meaningful changes at the patient level.[17] Individual patient-reported outcome score changes (responder definitions) over a predetermined time period that would be interpreted as treatment benefits can be used to assess treatment effects perceived as meaningful by the patient.[17,18]

Few studies have defined clinically meaningful score changes for patient-reported outcomes used in endometriosis.[19–22] Responder definitions were previously determined for EHP-30 subscales based on data from patients with moderate to severe pain associated with endometriosis in the ELARIS EM-I, and EM-II trials.[23] In the current post hoc analysis, responder definitions for EHP-30 subscales were applied to pooled ELARIS trial data[24] to determine whether treatment with elagolix, an oral nonpeptide gonadotropin-releasing hormone antagonist,[25] was associated with clinically meaningful improvements in HRQOL compared with placebo.

ROLE OF THE FUNDING SOURCE

METHODS

Data were pooled from two similar phase III randomized controlled trials, ELARIS EM-I (NCT01620528) and ELARIS EM-II (NCT01931670), which evaluated the efficacy and safety of elagolix for the treatment of moderate to severe pain associated with endometriosis.[24] The study designs and eligibility criteria have been previously described.[24] Briefly, premenopausal women aged 18–49 years who received a surgical diagnosis of endometriosis in the previous 10 years and who had moderate to severe pain associated with endometriosis were eligible for the studies. Participants were randomized 2:2:3 to receive elagolix 150 mg once daily (150-mg cohort), 200 mg twice daily (200-mg cohort), or placebo for 6 months with a 12-month follow-up period. The primary endpoints in the studies were the proportion of patients with a clinical response for dysmenorrhea and nonmenstrual pelvic pain at month 3 of treatment, where response was defined as clinically meaningful reduction in pain score, and decreased or stable use of rescue analgesics.[24] Secondary endpoints included efficacy evaluations per patient-reported outcomes, including assessment of HRQOL.

Patients in the two trials were administered the EHP-30 questionnaire[15] at baseline, and at months 1, 3, and 6 of treatment. The EHP-30 is a validated disease specific questionnaire with 30 questions that encompass five core scales: pain, control and powerlessness, emotional well-being, social support, and self-image.[15] The EHP-30 modular questionnaires address additional scales that may not apply to all women with endometriosis,[14,15] including the sexual intercourse scale, which was administered to patients in these trials. The EHP-30 questions are asked regarding endometriosis in the previous 4 weeks and are answered on a 5-point Likert scale, where 0=never, 1=rarely, 2=sometimes, 3=often, and 4=always. Raw scores for the questions within a scale are summed and transformed to a 0–100 scale, with higher scores indicating worse HRQOL.[14,15]

Least squares mean change from baseline to months 1, 3, and 6 was calculated for the pooled data set of patients. Differences between elagolix dose groups and placebo were derived from an analysis of covariance model, with treatment as the main effect and baseline value as a covariate. A triangulation approach was used to assess responder thresholds for the sexual relationship module and each domain of EHP-30. The triangulation methodology involved three psychometric approaches, anchor- and distribution-based analyses, and use of clinically relevant indicators (improvement in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia). The results for these three psychometric approaches as they apply to EHP-30 have been previously described.[23] The following responder definitions for EHP-30 scales were used: pain, 30-point reduction; control and powerlessness, 35-point reduction; emotional well-being, social

support, self-image, and sexual intercourse, 20-point reductions.[23] The percentages of patients who met the responder definitions for each of the six EHP-30 scales at months 1, 3, and 6 were determined.

A binary Poisson regression analysis was performed to determine the probability of patients meeting EHP-30 responder definitions at months 3 and 6. In this model, baseline EHP-30 scores and treatment arm were independent variables, and patients given placebo were used as the reference group. Relative risk (RR) estimates, 95% CIs, and associated P values were generated; regression results were adjusted for differences in baseline EHP-30 domain scores. Continuous variables were summarized by means and SD and categorical variables were reported as percentages. The EHP-30 data were reported for only nonmissing responses. All data analyses were performed using SAS 9.4.

An institutional review board at each study center approved the clinical study protocol before the study was conducted. Shulman Associates IRB conducted the majority of the institutional review board approvals at each study center. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines.[24] Informed consent was obtained from all individuals who participated in the ELARIS EM-I and EM-II trials.[24]

RESULTS

A total of 1,686 women were randomized and treated in the ELARIS EM-I and EM-II trials, with 734 receiving placebo, 475 receiving elagolix 150 mg once daily, and 477 receiving elagolix 200 mg twice daily (Table 1). The baseline demographics and clinical characteristics of the study populations were similar between trials and across treatment arms,[24] allowing data from both trials to be pooled by treatment arm. Baseline pain scores for dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia were highly similar between treatment arms (Table 1)[23,24]

Women in the elagolix 200-mg cohort had significant improvements from baseline in all six EHP-30 subscale scores compared with women in the placebo group at months 1, 3 and 6 of treatment (Table 2). In the elagolix 200-mg cohort, the greatest improvements compared with placebo (least squares mean difference±SE) were reported for pain (-21.09 ± 1.46; 95% CI -23.95 to -18.23; $P<.001$) and control and powerlessness (-23.10 ± 1.78; 95% CI -26.59 to -19.61; $P<.001$) at month 6. Improvements at month 6 were also reported

Table 1. Baseline Demographics and Clinical Characteristics of the Study Population

Parameter	Placebo (n=734)	Elagolix 150 mg Once Daily (n=475)	Elagolix 200 mg Twice Daily (n=477)
Age (y)	32.4±6.6	32.3±6.4	32.3±6.6
Race			
White	645 (87.9)	419 (88.2)	422 (88.5)
Black or African American	62 (8.4)	44 (9.3)	42 (8.8)
Other	27 (3.7)	12 (2.5)	13 (2.7)
BMI (kg/m²)*	27.7±6.3	27.6±6.6	27.4±6.6
Dysmenorrhea score†	2.16±0.46	2.16±0.48	2.13±0.49
Nonmenstrual pelvic pain score†	1.59±0.50	1.65±0.54	1.56±0.51
Dyspareunia score‡	1.48±0.83	1.50±0.85	1.49±0.86
Overall endometriosis-associated pain score (NRS)§	5.57±1.66	5.71±1.75	5.41±1.69
EHP-30 domain scores			
Pain	57.1±15.4	56.6±15.5	56.4±14.8
Control and powerlessness	65.9±21.2	67.3±22.2	65.7±21.8
Emotional well-being	47.2±20.2	48.1±20.9	48.3±20.1
Social support	51.7±26.4	53.1±26.4	53.9±25.8
Self-image	48.0±28.8	49.4±28.4	47.9±26.7
Sexual intercourse	61.9±25.4	60.2±26.7	62.0±24.6

BMI, body mass index; NRS, numeric rating scale; EHP-30, Endometriosis Health Profile-30.
Data are n (%) or mean±SD.
* BMI data were available for 731, 472, and 473 patients in the placebo, elagolix 150 mg once daily, and elagolix 200 mg twice daily cohorts, respectively.
† Pain responses were none=0, mild=1, moderate=2, and severe=3.
‡ Pain responses were none=0, mild=1, moderate=2, severe=3, and not applicable. Excluding women who responded, "not applicable," 606, 392, and 386 patients in the placebo, elagolix 150 mg once daily, and elagolix 200 mg twice daily groups, respectively, had baseline dyspareunia pain responses.
§ Response for overall endometriosis-associated pain ranged from 0 (no pain) to 10 (worst pain ever).

for the elagolix 150-mg cohort, but the magnitude was less than in the 200-mg cohort: pain (-10.70 ± 1.45; 95% CI -13.54 to -7.87; $P<.001$) and control and powerlessness (-9.93 ± 1.77; 95% CI -13.41 to -6.44; $P<.001$).

At month 1, a greater percentage of women treated with either dose of elagolix achieved responses for all EHP-30 subscales except sexual intercourse, compared with those given placebo (Fig. 1A–F). The percentage of patients meeting responder definitions increased from month 1 to month 3 for all EHP-30 subscales, with the greatest percentage of responders consistently in the elagolix 200-mg cohort (46.4–59.9%). By comparison, 38.1–44.0% of the elagolix 150-mg cohort and 25.5–37.9% of the placebo cohort met EHP-30 responder definitions at month 3. The placebo cohort had the lowest proportion of patients meeting responder definitions in the pain subscale at month 3 (25.5%; Fig. 1A). For both doses of elagolix, the percentage of patients meeting responder definitions at month 3 was greatest for the control and powerlessness subscale (150 mg, 44.0%; 200 mg, 59.9%; Fig. 1B). Among all EHP-30 subscales, the self-image subscale had the lowest proportion of patients meeting responder definitions for both elagolix doses at month 3 (150 mg, 38.1%; 200 mg, 46.4%; Fig. 1E).

From months 3–6, the percentage of patients in the placebo cohort who met responder definitions generally plateaued across subscales (Fig. 1A–F). In contrast, the percentage of patients in the elagolix 200-mg cohort who met responder definitions increased from month 3–6 for all subscales (52.7–66.0%). The percentages of patients in the elagolix 150-mg cohort who met responder definitions (37.2–50.1%) were relatively sustained from month 3–6 for pain, control and powerlessness, self-image, and sexual intercourse subscales. Increased proportions of patients in the elagolix 150-mg cohort were responders at month 6 for the emotional well-being (50.1%; Fig. 1C) and social support (43.7%; Fig. 1D) subscales compared with month 3 (43.3% and 39.3%, respectively).

At month 6, comparing all EHP-30 subscales, the self-image and sexual intercourse subscales had the fewest responders among the elagolix 150-mg cohort (both 37.2%; Fig. 1E and F). Similarly, the fewest patients in the elagolix 200-mg cohort met responder definitions at month 6 for the self-image subscale (52.7%; Fig. 1E).

A Poisson regression analysis with robust standard errors was performed to determine the effect of both elagolix doses compared with placebo on the probability of meeting EHP-30 responder definitions at months 3 and 6 of treatment. Unadjusted RRs and adjusted relative risks (aRRs) are provided in Tables 3 and 4, respectively.

After adjustment, the highest probability of meeting responder definitions was reported for the pain subscale at months 3 and 6 (Table 4). At month 3, patients in the elagolix 150-mg cohort had a 66% (aRR: 1.66; 95% CI 1.40–1.97; $P<.001$) greater

Table 2. Change From Baseline in Endometriosis Health Profile-30 Domain Scores

| Visit | EHP-30 Domain | LS Mean Change±SE | | |
		Placebo	Elagolix 150 mg Once Daily	Elagolix 200 mg Twice Daily
Month 1	Pain	-14.83 ± 0.70	-20.09 ± 0.86	-23.50 ± 0.87
	Control and powerlessness	-19.62 ± 0.86	-24.27 ± 1.07	-27.97 ± 1.08
	Emotional well-being	-9.94 ± 0.66	-13.18 ± 0.81	-14.00 ± 0.82
	Social support	-9.40 ± 0.80	-11.70 ± 0.99	-13.74 ± 1.00
	Self-image	-8.79 ± 0.79	-10.58 ± 0.98	-13.79 ± 0.99
	Sexual intercourse	-10.19 ± 0.87	-10.87 ± 1.06	-14.92 ± 1.09
Month 3	Pain	-18.49 ± 0.78	-26.79 ± 0.94	-35.59 ± 0.97
	Control and powerlessness	-24.86 ± 0.93	-32.81 ± 1.14	-42.28 ± 1.16
	Emotional well-being	-13.67 ± 0.75	-17.75 ± 0.92	-21.15 ± 0.94
	Social support	-12.54 ± 0.93	-18.00 ± 1.14	-24.14 ± 1.16
	Self-image	-11.16 ± 0.92	-16.54 ± 1.13	-21.08 ± 1.15
	Sexual intercourse	-13.54 ± 1.08	-17.22 ± 1.31	-25.85 ± 1.37
Month 6	Pain	-17.38 ± 0.93	-28.09 ± 1.11	-38.48 ± 1.12
	Control and powerlessness	-22.92 ± 1.14	-32.85 ± 1.36	-46.02 ± 1.37
	Emotional well-being	-13.68 ± 0.88	-20.33 ± 1.04	-26.50 ± 1.05
	Social support	-13.20 ± 1.13	-19.77 ± 1.35	-29.42 ± 1.36
	Self-image	-12.54 ± 1.09	-15.24 ± 1.31	-25.29 ± 1.31
	Sexual intercourse	-12.78 ± 1.35	-16.60 ± 1.56	-28.67 ± 1.58

EHP-30, Endometriosis Health Profile-30; LS, least squares.
P value for difference between elagolix doses and placebo was derived from an analysis of covariance model with treatment as the main effect and baseline value as a covariate.
* $P<.001$.
† $P<.01$.
‡ $P<.05$.

probability of meeting the pain subscale responder definition than those given placebo, and patients in the elagolix 200-mg cohort had a 137% (aRR 2.37, 95% CI 2.03–2.77; $P<.001$) greater probability than those given placebo. The probability of meeting the pain subscale responder definition at month 6 increased for both doses of elagolix; the probability for the elagolix 150-mg cohort was 75% (aRR 1.75, 95% CI 1.44–2.14; $P<.001$) greater than placebo and 169% (aRR 2.69, 95% CI 2.26–3.21; $P<.001$) greater than placebo for the elagolix 200-mg cohort. The probabilities of women in both elagolix dose cohorts meeting responder definitions for the control and powerlessness subscale were also significantly higher than the placebo cohort. At month 3, the probability of patients in the elagolix 150-mg cohort meeting the control and powerlessness subscale responder definition was 33% (aRR 1.33, 95% CI 1.14–1.54; $P<.001$) greater than placebo and 84% (aRR 1.84, 95% CI 1.62–2.10; $P<.001$) greater than placebo for patients in the elagolix 200-mg cohort. At month 6, probabilities were 50% (aRR 1.50, 95% CI 1.25–1.80; $P<.001$) and 129% (aRR 2.29, 95% CI 1.96–2.67; $P<.001$) greater than placebo for the elagolix 150-mg and 200-mg cohorts, respectively.

DISCUSSION

In this post hoc analysis, patients with moderate to severe pain associated with endometriosis who were treated with elagolix 150 mg once daily or 200 mg twice daily achieved clinically meaningful improvements in HRQOL in a dose-dependent manner, as observed for primary efficacy endpoints.[24] Higher percentages of patients in the elagolix 200-mg cohort met EHP-30 responder definitions than patients in the elagolix 150-mg cohort. At month 6, significant improvements from baseline were reported for all six subscale scores in the 200-mg cohort compared with placebo, and in four subscale scores (pain, control and powerlessness, emotional well-being, and social support) in the 150-mg cohort compared with placebo. Patients treated with elagolix perceived meaningful improvements in HRQOL as early as month 1 of treatment (200-mg cohort), with sustained or further improvements through months 3 and 6. Although both doses of elagolix increased the likelihood of meeting responder definitions across HRQOL domains compared with placebo, the RR estimates were greater in the 200-mg cohort. The changes in HRQOL scores mirror the improvements observed in pain scores dysmenorrhea and nonmenstrual pelvic pain.[24]

Patients treated with elagolix had the greatest probability of meeting responder definitions for pain

| Difference of LS Means From Placebo±SE (95% CI)	
Elagolix 150 mg Once Daily	Elagolix 200 mg Twice Daily
−5.26±1.10 (−7.43 to −3.10)*	−8.67±1.12 (−10.86 to −6.48)*
−4.65±1.37 (−7.35 to −1.96)*	−8.35±1.38 (−11.06 to −5.64)*
−3.23±1.04 (−5.28 to −1.19)†	−4.05±1.05 (−6.12 to −1.99)*
−2.30±1.28 (−4.81 to 0.20)	−4.35±1.28 (−6.87 to −1.83)*
−1.79±1.26 (−4.26 to 0.68)	−4.99±1.27 (−7.48 to −2.50)*
−0.68±1.37 (−3.37 to 2.01)	−4.73±1.40 (−7.48 to −1.99)*
−8.30±1.22 (−10.70 to −5.90)*	−17.10±1.25 (−19.54 to −14.66)*
−7.95±1.47 (−10.83 to −5.07)*	−17.42±1.49 (−20.34 to −14.49)*
−4.08±1.19 (−6.41 to −1.75)*	−7.48±1.21 (−9.85 to −5.11)*
−5.46±1.47 (−8.35 to −2.57)*	−11.60±1.49 (−14.52 to −8.67)*
−5.38±1.46 (−8.24 to −2.52)*	−9.92±1.47 (−12.80 to −7.03)*
−3.68±1.70 (−7.01 to −0.35)‡	−12.31±1.75 (−15.73 to −8.88)*
−10.70±1.45 (−13.54 to −7.87)*	−21.09±1.46 (−23.95 to −18.23)*
−9.93±1.77 (−13.41 to −6.44)*	−23.10±1.78 (−26.59 to −19.61)*
−6.65±1.36 (−9.32 to −3.97)*	−12.82±1.37 (−15.51 to −10.13)*
−6.57±1.76 (−10.03 to −3.11)*	−16.22±1.77 (−19.69 to −12.74)*
−2.69±1.70 (−6.04 to 0.65)	−12.74±1.70 (−16.08 to −9.40)*
−3.82±2.06 (−7.87 to 0.23)	−15.90±2.08 (−19.97 to −11.82)*
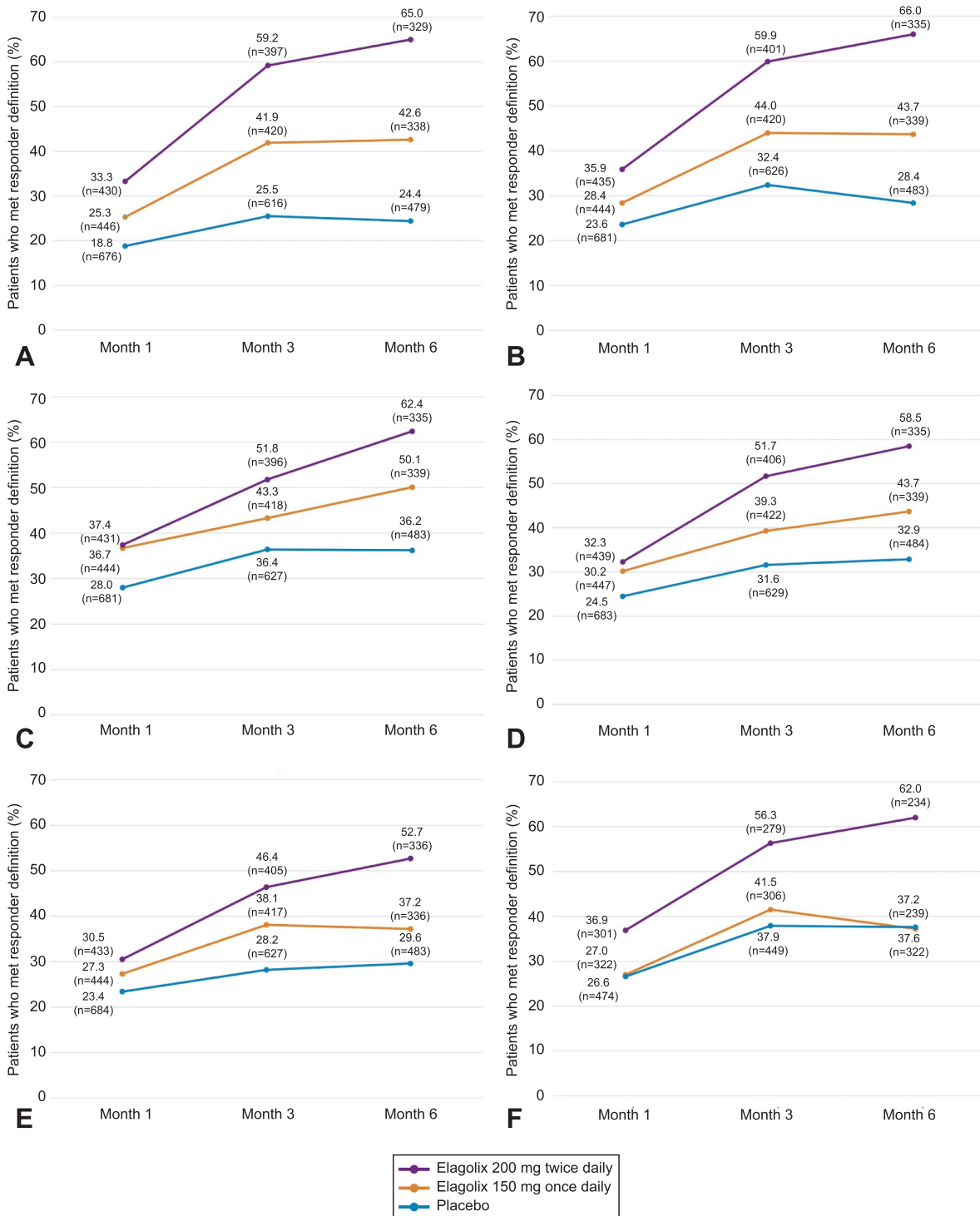
Fig. 1. Proportion of patients meeting responder definitions for EHP-30 (Endometriosis Health Profile-30) subscales at months 1, 3, and 6 of treatment. The percentages of patients who met responder definitions for the following EHP-30 subscales: pain (**A**), control and powerlessness (**B**), emotional well-being (**C**), social support (**D**), self-image (**E**), and sexual intercourse (**F**). n values indicate the total number of patients with EHP-30 scores for the indicated subscale at each timepoint per treatment arm. Responder definitions were based on the following reductions in subscale scores from baseline: pain, 30-point reduction; control and powerlessness, 35-point reduction; emotional well-being, social support, self-image, and sexual intercourse, 20-point reductions.

Taylor. Elagolix and Meaningful EHP-30 Improvements. Obstet Gynecol 2020.

Table 3. Unadjusted Poisson Relative Risk Estimates of Meeting Endometriosis Health Profile-30 Subscale Responder Definitions

Visit	EHP-30 Dimension	Elagolix 150 mg Once Daily vs Placebo [RR (95% CI)]	P	Elagolix 200 mg Twice Daily vs Placebo [RR (95% CI)]	P
Month 3	Pain	1.64 (1.38–1.96)	<.001	2.32 (1.98–2.72)	<.001
	Control and powerlessness	1.36 (1.16–1.59)	<.001	1.85 (1.61–2.12)	<.001
	Emotional well-being	1.19 (1.02–1.39)	.025	1.42 (1.24–1.64)	<.001
	Social support	1.24 (1.05–1.47)	.011	1.63 (1.41–1.90)	<.001
	Self-image	1.35 (1.13–1.61)	<.001	1.64 (1.40–1.94)	<.001
	Sexual intercourse	1.10 (0.92–1.31)	.315	1.49 (1.27–1.74)	<.001
Month 6	Pain	1.74 (1.43–2.13)	<.001	2.66 (2.23–3.18)	<.001
	Control and powerlessness	1.54 (1.28–1.86)	<.001	2.33 (1.98–2.73)	<.001
	Emotional well-being	1.38 (1.18–1.62)	<.001	1.72 (1.49–1.99)	<.001
	Social support	1.33 (1.11–1.59)	.002	1.78 (1.52–2.08)	<.001
	Self-image	1.26 (1.03–1.53)	.023	1.78 (1.50–2.11)	<.001
	Sexual intercourse	0.99 (0.80–1.23)	.935	1.65 (1.39–1.96)	<.001

EHP-30, Endometriosis Health Profile-30; RR, relative risk.

and control and powerlessness subscales. Elagolix results in clinically meaningful reductions in dysmenorrhea and nonmenstrual pelvic pain[24] and significantly reduces fatigue,[26] both of which likely contribute to clinically meaningful improvements in the control and powerlessness scale. The probability of meeting responder definitions was lowest for the sexual intercourse subscale. This

finding agrees with published data showing that treatment with elagolix 200-mg twice daily resulted in significant improvement in dyspareunia scores, whereas treatment with the 150-mg once-daily dose did not.[11]

Elagolix influences more than endometriosis-associated pain, as evidenced by the proportions of patients meeting responder definitions across EHP-30

Table 4. Adjusted Poisson Relative Risk Estimates of Meeting Endometriosis Health Profile-30 Subscale Responder Definitions

Visit	EHP-30 Dimension	Elagolix 150 mg Once Daily vs Placebo [RR (95% CI)]	P	Elagolix 200 mg Twice Daily vs Placebo [RR (95% CI)]	P
Month 3	Pain	1.66 (1.40–1.97)	<.001	2.37 (2.03–2.77)	<.001
	Control and powerlessness	1.33 (1.14–1.54)	<.001	1.84 (1.62–2.10)	<.001
	Emotional well-being	1.16 (1.01–1.34)	.042	1.39 (1.22–1.59)	<.001
	Social support	1.22 (1.04–1.43)	.013	1.57 (1.37–1.81)	<.001
	Self-image	1.33 (1.13–1.57)	<.001	1.69 (1.45–1.97)	<.001
	Sexual intercourse	1.11 (0.93–1.32)	.264	1.48 (1.27–1.73)	<.001
Month 6	Pain	1.75 (1.44–2.14)	<.001	2.69 (2.26–3.21)	<.001
	Control and powerlessness	1.50 (1.25–1.80)	<.001	2.29 (1.96–2.67)	<.001
	Emotional well-being	1.35 (1.16–1.57)	<.001	1.67 (1.45–1.92)	<.001
	Social support	1.30 (1.09–1.53)	.003	1.70 (1.47–1.97)	<.001
	Self-image	1.22 (1.01–1.47)	.036	1.80 (1.54–2.11)	<.001
	Sexual intercourse	1.00 (0.81–1.24)	.988	1.62 (1.36–1.92)	<.001

EHP-30, Endometriosis Health Profile-30; RR, relative risk.
Regression results were adjusted for differences in baseline EHP-30 domain scores.

subscales. Endometriosis is associated with feelings of powerlessness and the sense that symptoms dominate one's life.[5,15,27] Effective symptom management with elagolix may restore a sense of control and improve emotional well-being by reducing depression, anxiety, and hopelessness.[5,27] Treatment of endometriosis with elagolix may allow women to more fully engage in social activities and relationships, which often suffer owing to endometriosis symptoms.[5,27] Alleviation of dyspareunia by elagolix improves women's sexual quality of life,[11] positively influencing intimate relationships that may have deteriorated.[5,27] It is common for women with endometriosis to defer or lose opportunities for career or educational advancement[5,7,12,27,28]; however, elagolix was shown to restore women's workplace productivity.[26] The ability to participate in the workforce promotes mental well-being[29] and reduces the financial burden of endometriosis.[12] In these ways, elagolix mitigates the effects of endometriosis on women's HRQOL.

This study evaluated the effect of a standardized treatment regimen on clinically meaningful improvements in EHP-30 scores in women with moderate to severe endometriosis-associated pain. A PubMed search for "endometriosis EHP-30" found two other studies that evaluated clinically meaningful changes in EHP-30 scores. One study surveyed only 40 women with endometriosis who were recruited from one medical center before and after surgical intervention.[22] The second study evaluated clinically meaningful score changes in the Dutch EHP-30 among Dutch women with endometriosis who were recruited from a medical center and patient support group who received various treatments.[19] In contrast, our study highlights the utility of applying EHP-30 responder definitions to measure therapeutic efficacy in a large clinical trial setting.

A strength of this analysis is the large sample size derived from two phase III randomized, double-blind placebo-controlled trials. A high percentage of patients given placebo met responder definitions across EHP-30 subscales (28–38%). This placebo effect is not uncommon in a disease in which pain is the primary symptom, and the results of this analysis reflect placebo response rates observed for the trials' primary endpoints.[24] Despite this, regression analyses found significantly higher probabilities of meeting responder definitions for patients treated with elagolix than for those who were given placebo. The responder definitions used here were based on a patient population with moderate to severe pain associated with endometriosis and are not applicable to patients with milder endometriosis. The EHP-30 responses may be subject to recall bias; however, recall was limited to the previous 4 weeks. Additional studies are needed to access whether the effects of elagolix are sustained long-term, because the present analysis was limited to 6 months.

In summary, this analysis demonstrated that the treatment of women with moderate to severe pain associated with endometriosis with elagolix 150 mg once daily or 200 mg twice daily resulted in greater HRQOL improvements than placebo that were clinically meaningful to patients. Treatment with elagolix 200 mg twice daily was associated with a higher chance of meeting responder definitions across EHP-30 scales than elagolix 150 mg once daily. These improvements are expected to positively affect the personal and professional lives of women with endometriosis.

REFERENCES

1. Johnson NP, Hummelshoj L; World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. Hum Reprod 2013;28:1552–68.

2. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005;20:2698–704.

3. Armstrong C. ACOG updates guideline on diagnosis and treatment of endometriosis. Am Fam Physician 2011;83:84–5.

4. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. Hum Reprod 2014;29:400–12.

5. Culley L, Law C, Hudson N, Denny E, Mitchell H, Baumgarten M, et al. The social and psychological impact of endometriosis on women's lives: a critical narrative review. Hum Reprod Update 2013;19:625–39.

6. Fourquet J, Baez L, Figueroa M, Iriarte RI, Flores I. Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. Fertil Steril 2011;96:107–12.

7. Fourquet J, Gao X, Zavala D, Orengo JC, Abac S, Ruiz A, et al. Patients' report on how endometriosis affects health, work, and daily life. Fertil Steril 2010;93:2424–8.

8. Nnoaham KE, Hummelshoj L, Webster P, d'Hooghe T, de Cicco Nardone F, de Cicco Nardone C, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril 2011;96:366–73.e8.

9. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod 2012;27:1292–9.

10. Bernuit D, Ebert AD, Halis G, Strothmann A, Gerlinger C, Geppert K, et al. Female perspectives on endometriosis: findings from the uterine bleeding and pain women's research study. J Endometr 2011;3:73–85.

11. Leyland N, Taylor HS, Archer DF, Peloso PM, Soliman AM, Palac HL, et al. Elagolix reduced dyspareunia and improved health-related quality of life in premenopausal women with endometriosis-associated pain. J Endometr Pelvic Pain Disord 2019;11:171–80.

12. Soliman AM, Coyne KS, Gries KS, Castelli-Haley J, Snabes MC, Surrey ES. The effect of endometriosis symptoms on absenteeism and presenteeism in the workplace and at home. J Manag Care Spec Pharm 2017;23:745–54.

13. Bourdel N, Chauvet P, Billone V, Douridas G, Fauconnier A, Gerbaud L, et al. Systematic review of quality of life measures in patients with endometriosis. PLoS One 2019;14:e0208464.

14. Jones G, Jenkinson C, Taylor N, Mills A, Kennedy S. Measuring quality of life in women with endometriosis: tests of data quality, score reliability, response rate and scaling assumptions of the Endometriosis Health Profile questionnaire. Hum Reprod 2006;21:2686–93.

15. Jones G, Kennedy S, Barnard A, Wong J, Jenkinson C. Development of an endometriosis quality-of-life instrument: the Endometriosis Health Profile-30. Obstet Gynecol 2001;98:258–64.

16. Johnston BC, Ebrahim S, Carrasco-Labra A, Furukawa TA, Patrick DL, Crawford MW, et al. Minimally important difference estimates and methods: a protocol. BMJ Open 2015;5:e007953.

17. U.S. Department of Health and Human Services,Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry 2009. Patient-reported outcome measures: use in medical product development to support labeling claims. Available at: https://www.fda.gov/media/77832/download. Retrieved November 8, 2019.

18. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. Expert Rev Pharmacoecon Outcomes Res 2011;11:163–9.

19. van de Burgt TJ, Kluivers KB, Hendriks JC. Responsiveness of the Dutch Endometriosis Health Profile-30 (EHP-30) questionnaire. Eur J Obstet Gynecol Reprod Biol 2013;168:92–4.

20. Gerlinger C, Schumacher U, Faustmann T, Colligs A, Schmitz H, Seitz C. Defining a minimal clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: analyses of two placebo-controlled, randomized trials. Health Qual Life Outcomes 2010;8:138.

21. Wickstrom K, Edelstam G. Minimal clinically important difference for pain on the VAS scale and the relation to quality of life in women with endometriosis. Sex Reprod Healthc 2017;13:35–40.

22. Jones G, Jenkinson C, Kennedy S. Evaluating the responsiveness of the Endometriosis Health Profile questionnaire: the EHP-30. Qual Life Res 2004;13:705–13.

23. Pokrzywinski R, Soliman AM, Chen J, Snabes MC, Taylor HS, Coyne KS. Responsiveness evaluation and recommendation for responder thresholds for Endometriosis Health Profile-30: analysis of two phase III clinical trials. J Womens Health (Larchmt) 2020;20:253–61.

24. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med 2017;377:28–40.

25. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. J Clin Endocrinol Metab 2017;102:1683–91.

26. Surrey ES, Soliman AM, Agarwal SK, Snabes MC, Diamond MP. Impact of elagolix treatment on fatigue experienced by women with moderate to severe pain associated with endometriosis. Fertil Steril 2019;112:298–304.e3.

27. Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on women's lives: a qualitative study. BMC Womens Health 2014;14:123.

28. De Graaff AA, D'Hooghe TM, Dunselman GA, Dirksen CD, Hummelshoj L, WERF EndoCost Consortium, et al. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. Hum Reprod 2013;28:2677–85.

29. Schuring M, Robroek SJ, Burdorf A. The benefits of paid employment among persons with common mental health problems: evidence for the selection and causation mechanism. Scand J Work Environ Health 2017;43:540–9.

PEER REVIEW HISTORY