Impact of elagolix treatment on fatigue experienced by women with moderate to severe pain associated with endometriosis

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Objective: To evaluate the efficacy of elagolix, an oral GnRH antagonist, for the reduction of fatigue in women with moderate or severe endometriosis-associated pain.
Design: Randomized, double-blind, multicenter, placebo-controlled phase III trial.
Setting: Clinics.
Patient(s): A total of 860 women treated with elagolix or placebo.
Intervention(s): Women received either elagolix at 150 mg daily (QD) orally, elagolix at 200 mg twice daily (BID) orally, or placebo.
Main Outcome Measure(s): Change from baseline to month 1, 3, and 6 visits, in Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 6a questionnaire T-scores.
Results(s): At baseline, 54%–74% of women with moderate to severe pain associated with endometriosis reported having fatigue-related issues "quite a bit" or "very much," depending on the question asked. Fatigue extent was reduced to 29%–43% and 14%–29% for women treated with elagolix at 150 mg QD and 200 mg BID, respectively, at 6 months, compared with 35%–50% with placebo. The resultant decrease in fatigue T-scores was significant after elagolix treatment compared with placebo at 6 months, with changes of −2.21 and −5.90 with elagolix at 150 mg QD and 200 mg BID, respectively. Significant reduction in fatigue scores were observed among patients reporting clinically meaningful response "reduction" in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia (−7.31, −6.62, and −4.31, respectively) compared with nonresponders.
Conclusion(s): In women with moderate to severe endometriosis related pain, elagolix significantly reduces fatigue levels. (Fertil Steril® 2019;112:298–304. ©2019 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, fatigue, elagolix, gonadotropin-releasing hormone antagonist

Endometriosis is a chronic estrogen-dependent disorder that affects 6%–10% of women of reproductive age (1, 2). It is characterized by the presence of endometrial-like tissue outside of the uterus (1, 2). Women with endometriosis typically suffer from dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia, as well as infertility (1–3). Additional symptoms that they may encounter include pain due to dyschezia and painful urination (1–3). As a consequence of these symptoms, women with endometriosis have a reduced quality of life with psychologic problems and difficulties in personal relationships (4–6).

One additional and especially problematic aspect of endometriosis, which has been reported to occur in ~50%–87% of women with the disease, is the burden of fatigue

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(7–12). For many women, fatigue is considered one of the more intense symptoms of endometriosis (9, 10). In women with endometriosis, fatigue is associated with insomnia, depression, pain, and occupational stress (7). Furthermore, endometriosis-associated fatigue can lead to a decreased ability to perform at work, impairment of normal physical and social activities, and reduced quality of life (8, 9, 13).

Elagolix is an oral nonpeptide GnRH antagonist that provides dose-dependent suppression of E_2 production and has been recently approved in the United States for the management of moderate to severe pain associated with endometriosis (14, 15). In two phase III studies, ELARIS Endometriosis I and II (EM-I [NCT01620528] and EM-II [NCT01931670]), elagolix significantly improved dysmenorrhea and nonmenstrual pelvic pain during the 6-month treatment period for women with moderate or severe endometriosis-associated pain (16). In the EM-1 trial, 46.6% and 75.8% of women had a clinical response with respect to dysmenorrhea for the lower and higher dosages of elagolix, respectively, compared with 19.6% for placebo at 3 months ($P<.001$) (16). Furthermore, a clinical response with respect to nonmenstrual pelvic pain was achieved in 50.4% and 54.5% of women receiving the lower and higher dosages of elagolix, respectively, compared with 36.5% for placebo at 3 months ($P<.001$) (16). Adverse events reported in these studies included hypoestrogenic effects, including hot flushes and changes in bone mineral density and lipid levels (16).

In the present report, we extend the results of these phase III studies to describe changes in fatigue and its association with endometriosis symptom improvement in women with moderate or severe endometriosis-associated pain.

MATERIALS AND METHODS

Study Design and Participants

EM-I was a randomized, double-blind, multicenter, placebo-controlled phase III trial that enrolled women from 151 sites in the United States and Canada (16). The study started on May 22, 2012, and was completed on September 28, 2015. The study consisted of four segments: 1) a washout of hormonal therapies (if applicable); 2) a screening period of up to 100 days; 3) a 6-month treatment period; and 4) a follow-up period of up to 12 months, unless the woman was enrolled in the corresponding 6-month extension period. During the screening period, which encompassed at least two menstrual cycles, women switched analgesic agents to receive a nonsteroidal antiinflammatory drug (500 mg naproxen), an opioid according to country (eg, 5 mg hydrocodone plus 325 mg acetaminophen), or both. Details on allowed rescue medication have been previously published (16).

Enrollment criteria for EM-I have been previously reported (16). The study included premenopausal women aged 18–49 years who had a surgical diagnosis of endometriosis in the previous 10 years and moderate to severe endometriosis-associated pain. Exclusion criteria included: z-score of less than −1.5 for bone mineral density at the lumbar spine, femoral neck, or total hip at screening; clinically significant gynecologic conditions; and chronic pain conditions unrelated to endometriosis.

Fatigue was measured with the use of a Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 6a questionnaire (17–20). The PROMIS questionnaire was developed as a multicenter collaborative project funded by the National Institutes of Health to improve measurements of symptoms and outcomes, including fatigue (18–20). The PROMIS Fatigue Short Form 6a questionnaire is composed of 6 questions to evaluate the severity of fatigue during the previous 7 days (listed in Supplemental Figs. 1 and 2, available online at www.fertstert.org) (19). Women can answer the questions with "not at all," "a little bit," "somewhat," quite a bit," or "very much." Results from the PROMIS Fatigue Short Form 6a questionnaire were consistent with other measures of fatigue, the Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F) and the SF-36v2 Vitality subscale (18).

An Institutional Review Board (IRB) at each study center approved the clinical study protocol before the study was conducted. Shulman Associates IRB conducted the majority of the IRB approvals (approval number 201202559; approval date April 11, 2012). The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines. Written consents were provided by all of the women participating in the trial.

Treatments

Treatment details have been published previously (16). Briefly, women were randomized 2:2:3 to receive either elagolix at 150 mg daily (QD) orally, elagolix at 200 mg twice daily (BID) orally, or placebo. Treatment lasted for 6 months with trial visits performed on day 1 and monthly through month 6.

Outcomes

The secondary efficacy variable reported from this study was change from baseline to each visit (months 1, 3, and 6) in PROMIS Fatigue Short Form 6a questionnaire T-scores. Each question had a raw score from 1 (not at all) to 5 (very much) with a total raw score ranging from 6 to 30. Raw scores were converted to T-scores, a standardized score with a mean of 50 and a standard deviation of 10. Higher T-scores indicate more fatigue (less desirable). Fatigue analysis was also performed for women who entered the extension studies for EM-1 (EM-III; NCT01760954) (21) and were treated for a total of 12 months with elagolix at 150 mg QD or 200 mg BID.

The study also reported baseline predictors of fatigue scores and the relationship between changes in fatigue scores to the clinical responder status for endometriosis symptoms dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia. Clinical response was defined as a clinically meaningful reduction in pain score (on a scale from 0 [no pain] to 3 [severe pain]) and a decrease in or stable use of rescue analgesic agents as recorded in a daily electronic diary (16).

Statistical Analysis

Results from the PROMIS Fatigue Short Form 6a were summarized with the mean, standard deviation, median, and range for each treatment group determined. Change from baseline

TABLE 1

Change from baseline in PROMIS Fatigue Questionnaire T-scores during the treatment period (modified intention-to-treat).

Measure	Placebo	Elagolix 150 mg QD	Elagolix 200 mg BID
Baseline			
No. of women	371	246	243
Mean (SD)	62.37 (7.82)	64.16 (7.71)	63.93 (7.46)
Median (interquartile range [IQR])	62.40 (57.50–67.80)	65.00 (60.00–67.80)	65.00 (60.00–67.80)
LS means (SE)	62.37 (0.40)	64.16 (0.49)	63.93 (0.49)
Month 1			
No. of women	350	227	223
Mean (SD)	59.41 (9.09)	59.53 (9.34)	57.80 (9.02)
Median (IQR)	60.00 (53.70–65.00)	60.00 (53.70–65.00)	57.50 (52.40–63.70)
Difference from baseline			
No. of women	348	224	219
LS means (SE)	−3.27 (0.42)	−4.28 (0.53)	−5.54 (0.53)
Difference of LS means from placebo (SE, 95% CI)	–	−1.01 (0.68, −2.34 to 0.32)	−2.27 (0.68, −3.60 to −0.93)
P value	–	.069	<.001
Month 3			
No. of women	316	219	202
Mean (SD)	58.22 (9.65)	57.40 (9.55)	54.48 (9.55)
Median (IQR)	58.80 (52.40–63.70)	57.50 (50.90–63.70)	55.10 (47.80–61.20)
Difference from baseline			
No. of women	314	216	198
LS means (SE)	−4.61 (0.50)	−6.26 (0.60)	−8.84 (0.63)
Difference of LS means from placebo (SE, 95% CI)	–	−1.66 (0.79, −3.20 to −0.11)	−4.23 (0.81, −5.82 to −2.65)
P value	–	.018	<.001
Month 6			
No. of women	248	172	165
Mean (SD)	58.33 (10.00)	56.80 (9.49)	52.73 (10.01)
Median (IQR)	58.80 (52.40–65.00)	56.30 (49.40–65.00)	52.40 (47.80–60.00)
Difference from baseline			
No. of women	246	170	161
LS means (SE)	−4.53 (0.59)	−6.73 (0.71)	−10.42 (0.73)
Difference of LS means from placebo (SE, 95% CI)	–	−2.21 (0.92, −4.02 to −0.40)	−5.90 (0.94, −7.74 to −4.06)
P value	–	.008	<.001

Note: BID = twice daily; CI = confidence interval; IQR = interquartile range; LS = least-squares; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily; SE = standard error.

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in PROMIS Fatigue Short Form 6a scores was evaluated and compared between each elagolix dosing group and placebo by means of one-way analysis of covariance with the use of treatment as main factor and baseline as covariate. We calculated least-squares means, treatment difference in least-squares means, 95% confidence intervals (CIs), and *P* values. The analysis used a multivariate regression to estimate the impact of baseline characteristics and pain levels associated with baseline fatigue scores for comparison of endometriosis symptoms in clinical responders versus nonresponders regarding improvements in fatigue scores.

Analyses were performed in the modified intention-to-treat population, which included all of the women who underwent randomization and received at least one dose of elagolix or placebo. SAS version 9.1.3 or later (SAS Institute, Cary, North Carolina) was used for the analyses.

RESULTS

Fatigue at Baseline in Women with Endometriosis

The study evaluated a total of 371, 246, and 243 women treated with placebo, 150 mg QD elagolix, and 200 mg BID elagolix, respectively. As reported previously, baseline demographics and clinical characteristics were similar between the treatment groups (16). The treatment arms had almost identical dysmenorrhea scores (2.2 [SD 0.4–0.5]), nonmenstrual pelvic pain scores (1.6 [SD 0.5]), and dyspareunia scores (1.5–1.6 [SD 0.8–0.9]) (16). The baseline responses to the six individual PROMIS Fatigue Short Form 6a questions/statements showed that ≥54% of respondents noted having fatigue-related issues "quite a bit" or "very much" (Supplemental Figs. 1 and 2). In particular, for the statement "I feel fatigued," 74% of respondents selected "quite a bit" or "very much" as a response (Supplemental Figs. 1 and 2).

In this study, T-scores at baseline ranged from 33.4 to 76.8. Median T-scores for the combined scores ranged from 62.4 to 65.0 at baseline, which is more than 1 standard deviation higher than the population average, reflecting the significant fatigue experienced by the endometriosis population (Table 1) (19). At baseline, the three main symptoms of endometriosis were associated independently with an increase in fatigue score among patients. The greatest effect (coefficient estimate [SE]) was observed for nonmenstrual pelvic pain (1.61 [0.73]), followed by dyspareunia (1.29 [0.40]) and dysmenorrhea (1.04 [0.75]; Table 2).

TABLE 2

Predictors of fatigue scores at baseline (modified intention-to-treat).

Factor	Coefficient estimate (SE)	*P* value
Body mass index	−0.00 (0.05)	.930
Age	0.12 (0.05)	.014
Dysmenorrhea	1.04 (0.75)	.163
Nonmenstrual pelvic pain	1.61 (0.73)	.029
Dyspareunia	1.29 (0.40)	.001
Tobacco use		
Current vs. never	1.25 (0.70)	.073
Former vs. never	−0.19 (0.78)	.808
Stage of endometriosis at diagnosis		
Stage 2 vs. stage 1	1.98 (1.18)	.095
Stage 3 vs. stage 1	0.66 (1.34)	.623
Stage 4 vs. stage 1	1.77 (1.30)	.174
Unknown vs. stage 1	0.68 (0.90)	.453
Alcohol use		
User vs. never	0.28 (0.79)	.723
Ex-user vs. never	1.20 (1.25)	.338
Intercept	51.75 (2.58)	< .001

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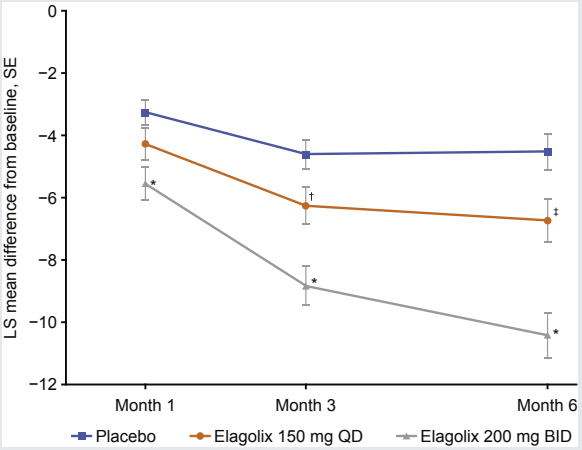
FIGURE 1



Change from baseline in PROMIS Fatigue Questionnaire T-scores at months 1, 3, and 6 of treatment (modified intention-to-treat). N values (placebo/elagolix 150 QD/elagolix 200 BID): month 1: 348/224/219; month 3: 314/216/198; month 6: 246/170/161. *P* value vs. placebo: *<.001; †<.01; ‡<.05. BID = twice daily; LS = least squares; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily; SE = standard error.

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Elagolix Reduced Fatigue Scores in Women in a Dose-Dependent Manner

Responses of "quite a bit" or "very much" to the six individual questions/statements in PROMIS at baseline was 58%–79% and 56%–79% for the 150 mg QD and 200 mg BID elagolix groups, respectively, and decreased at 3 months to 29%–43% and 18%–34%, respectively (Supplemental Figs. 1 and 2). For women receiving placebo, at 3 months 31%–48% women gave these responses compared with 49%–68% at baseline (Supplemental Figs. 1 and 2). At 6 months, "quite a bit" or "very much" responses decreased further with elagolix treatment (29%–43% and 14%–29% of women treated with elagolix at 150 mg QD and 200 mg BID, respectively), with 35%–50% of women treated with placebo giving this response (Supplemental Figs. 1 and 2).

A significant decrease in fatigue was observed with elagolix treatment compared with placebo based on T-scores of the PROMIS responses at both 3 and 6 months in a dose-dependent manner (Fig. 1; Supplemental Fig. 3 [available online at www.fertstert.org]; Table 1). At 3 months, there was a decrease of 1.66 (95% CI −3.20 to −0.11; $P=.018$) and 4.23 (95% CI −5.82 to −2.65; $P<.001$) with 150 mg QD and 200 mg BID elagolix, respectively, compared with placebo (Fig. 1; Table 1). This decrease in fatigue was greater at 6 months with elagolix at 150 mg QD (−2.21, 95% CI −4.02 to −0.40; $P=.008$) and 200 mg BID (−5.90, 95% CI −7.74 to −4.06; $P<.001$) compared with placebo (Fig. 1; Table 1). The impact of elagolix on reducing fatigue scores was sustained after 12 months of treatment. The mean PROMIS T-scores after 12 months of elagolix treatment in the extension study were similar to those observed at 6 months (EM-III [12 mo] vs. EM-1 [6 mo]: 150 mg QD: 55.66 vs. 56.97; 200 mg BID: 51.79 vs. 53.40) for women who participated in both studies (Supplemental Table 1, available online at www.fertstert.org).

A strong relationship was observed between achieving a clinical response in endometriosis pain symptoms and fatigue improvement (Table 3). Women who achieved a clinical meaningful response in dysmenorrhea, nonmenstrual pelvic pain, or dyspareunia had significant improvements in their fatigue scores compared with nonresponders: −5.41, −6.14, and −3.72, respectively, at 3 months and −7.31, −6.62, and −4.31, respectively, at 6 months (all $P<.001$; Table 3). A similar relationship was observed when this analysis was repeated among women receiving either dose of elagolix (Supplemental Table 2, available online at www.fertstert.org).

DISCUSSION

Fatigue is a well recognized symptom of endometriosis that is associated with insomnia, depression, pain, and occupational stress (7–9, 13, 22, 23). In women with endometriosis, fatigue can lead to serious physical, psychologic, and health-related quality of life issues (7–9, 13). In this report we present the level of fatigue that women with endometriosis who participated in the ELARIS EM-I study had and the improvements in fatigue they achieved with the use of elagolix.

We found that at baseline, a large proportion of women with endometriosis expressed having a significant degree of fatigue and gave a high proportion of negative responses to questions on the PROMIS Fatigue Short Form 6a questionnaire. More than 60% of women gave a response of "quite a bit" or "very much" to the questions or statements that dealt with how fatigued they were, how bothersome their fatigue was, and how run-down they felt. For more than one-half of the women in the study, fatigue resulted in difficulty initiating activities and interfered with their physical functioning. Overall, based on the responses to these questions, 17%

TABLE 3

Relationship between responder status for endometriosis symptoms on change in fatigue scores among all patients (modified intention-to-treat).

			Fatigue score change from baseline: responder vs. nonresponder	
Symptom	**Mean fatigue score**	***P* value**	**Adjusted difference (SE)**	***P* value**
Dysmenorrhea				
Month 3				
Responder (n = 326)	54.10	<.001	−5.41 (0.64)	<.001
Nonresponder (n = 410)	59.21			
Month 6				
Responder (n = 268)	52.35	<.001	−7.31 (0.74)	<.001
Nonresponder (n = 316)	59.61			
Nonmenstrual pelvic pain				
Month 3				
Responder (n = 362)	54.00	<.001	−6.14 (0.63)	<.001
Nonresponder (n = 374)	59.80			
Month 6				
Responder (n = 293)	52.97	<.001	−6.62 (0.75)	<.001
Nonresponder (n = 291)	59.61			
Dyspareunia				
Month 3				
Responder (n = 218)	55.12	<.001	−3.72 (0.75)	<.001
Nonresponder (n = 327)	58.69			
Month 6				
Responder (n = 180)	53.95	<.001	−4.31 (0.91)	<.001
Nonresponder (n = 240)	58.51			

Note: Clinical response was defined as a clinically meaningful reduction in pain score (on a scale from 0 [no pain] to 3 [severe pain]) and a decrease in or stable use of rescue analgesic agents as recorded in a daily electronic diary (16). Models were controlled for baseline fatigue scores.

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and 57% of women at baseline had a severe or moderate level of fatigue, respectively.

The percentage of women with fatigue observed in this study was consistent with results from an earlier study of women with endometriosis from Switzerland, Germany, and Austria. In that study, 50.7% reported frequent fatigue compared with 22.4% of matched control subjects (7). Other studies have reported fatigue in 72%–87% of women with endometriosis (9, 11, 12).

We observed that each main symptom of endometriosis (dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia) had an individual impact on increasing fatigue among patients at baseline. Treatments that address several of these symptoms can therefore be expected to significantly ameliorate fatigue scores. This was observed in the present trial. As reported previously, elagolix treatment results in significant clinical improvements in endometriosis symptoms (all main symptoms with 200 mg BID and dysmenorrhea and nonmenstrual pelvic pain with 150 mg QD) (16).

Elagolix treatment resulted in significant improvements in fatigue scores compared with placebo, which began as early as month 1 for the 200 mg BID dosage and month 3 for the 150 mg QD dosage and was maintained through month 6. Furthermore, improvement in fatigue was greater for women who had a clinically meaningful response in the three main symptoms of endometriosis—dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia—compared with nonresponders.

Currently, the first-line therapy recommended to treat endometriosis is the use of nonsteroidal antiinflammatory drugs or other analgesics and combined oral contraceptive pills and progestins (3). Recommended second-line therapies include GnRH agonists, such as leuprolide acetate, with add-back hormone replacement therapy (3). However, to the best of our knowledge, the effect of these treatments on reducing fatigue have not been reported. Conversely, one report indicated that fatigue was an adverse event associated with the GnRH agonist leuprolide acetate itself (24).

There are limitations associated with this study. No determination of the level of fatigue at baseline relative to matched controls was performed, because this analysis was based on a clinical trial study of elagolix in women with moderate to severe endometriosis. The present study focused on the effect of endometriosis on fatigue and did not evaluate the effect of confounding factors, such as the influence of other diseases, on fatigue. The influence of confounding factors among the cohorts in this study was assumed to be balanced through the randomization process and by controlling for baseline fatigue scores when conducting group comparisons. Also, this study was not designed to compare the different elagolix dose regimens to each other. The clinical meaningfulness of improvements in fatigue with elagolix treatment observed in this study remains to be determined. Such determination would require an estimation of the minimal important difference by means of triangulation of methods (anchor-based and distribution-based methods, etc.), which was beyond the scope of the present study. Furthermore, owing to more sporadic measurement of E_2 levels in the initial trials, a specific relationship between E_2 suppression and relief of fatigue could not be evaluated. The ability to assess the relationship between symptom relief and fatigue reduction within each of the elagolix arms was limited; the small number of patients for whom data could be analyzed reduced the statistical power. Finally, as with all studies of this nature, questionnaire responses were subjective and susceptible to recall bias.

CONCLUSION

The results presented in this study expand the benefits of treating women with endometriosis with the use of elagolix. Elagolix, in addition to significantly reducing dysmenorrhea and nonmenstrual pain in women with endometriosis, provides significant lessening of fatigue, a relevant symptom of this disease.

DATA-SHARING STATEMENT

Abbvie is committed to responsible data sharing regarding the clinical trials we sponsor. Access is provided to anonymized patient- and trial-level data (analysis data sets), as well as other information (eg, protocols and clinical study reports) from Abbvie-sponsored phase II–IV global interventional clinical trials conducted in patients (completed as of May 2004 for products and indications approved in either the United States or the European Union), as long as the trials are not part of an ongoing or planned regulatory submission). This includes requests for clinical trial data for unlicensed products and indications.

Access to these clinical trial data can be requested by any qualified researchers who engage in rigorous independent scientific research and will be provided after review and approval of a research proposal and statistical analysis plan and execution of a data-sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

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Impacto del tratamiento con elagolix en la fatiga experimentada por las mujeres con dolor moderado a intenso asociado con la endometriosis

Objetivo: Evaluar la eficacia de elagolix, un antagonista oral de la GnRH, para la reducción de la fatiga en mujeres con dolor asociado a la endometriosis.

Diseño: Ensayo aleatorizado, doble ciego, multicéntrico y controlado con placebo en fase III.

Configuración: Clínicas.

Paciente(s): Un total de 860 mujeres tratadas con elagolix o placebo.

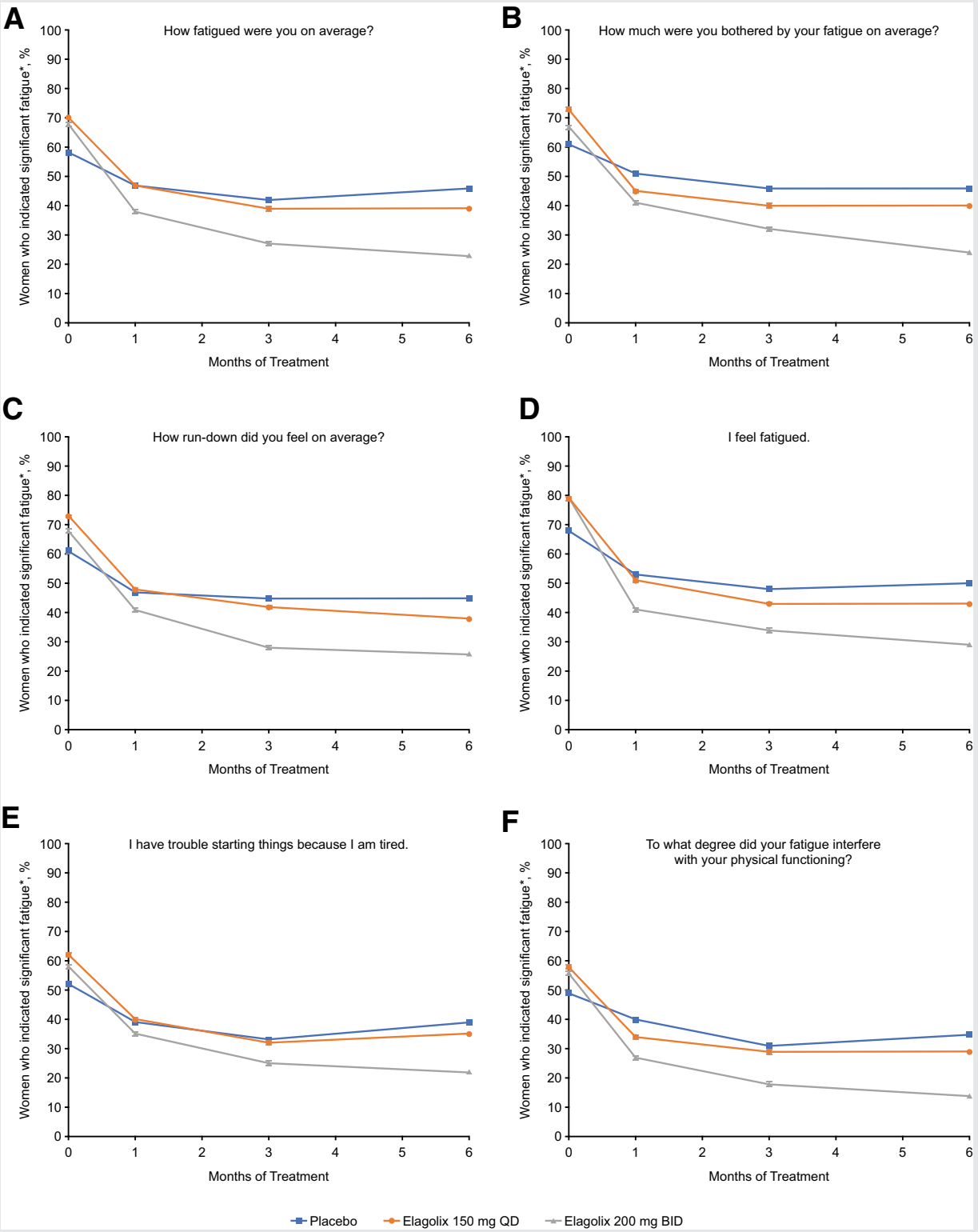
Intervención(es): Las mujeres recibieron elagolix 150 mg diarios (QD) por vía oral, elagolix 200 mg dos veces al día por vía oral (BID), o placebo.

Medidas de resultados principales: Los cambios en la Información de medición de resultados informados por la paciente Sistema (PROMIS), Fatigue Short Form 6a questionnaire T-scores, desde la visita basal a los meses 1, 3 y 6.

Resultados: Al inicio, 54%-74% de las mujeres con dolor moderado a intenso asociado con endometriosis informaron tener problemas relacionados con la fatiga como ''un poco'' o '' mucho'', dependiendo de la pregunta planteada. La extensión de la fatiga se redujo al 29%–43% y al 14%–29% para mujeres tratadas con elagolix a 150 mg QD y 200 mg BID, respectivamente, a los 6 meses, en comparación con 35%–50% con Placebo. La disminución del T-score de fatiga fue significativa después del tratamiento con elagolix en comparación con placebo a los 6 meses, con cambios de -2,21 y - 5,90 con elagolix a 150 mg QD y 200 mg BID, respectivamente. Se observó una reducción significativa del escore de fatiga en las pacientes que informaron una disminución clínicamente significativa en dismenorrea, dolor pélvico no menstrual, y dispareunia (-7,31, -6,62 y -4,31, respectivamente) en comparación con las no respondedoras.

Conclusión(s): En mujeres con dolor relacionado con endometriosis de moderada a grave, elagolix reduce significativamente los niveles de fatiga.

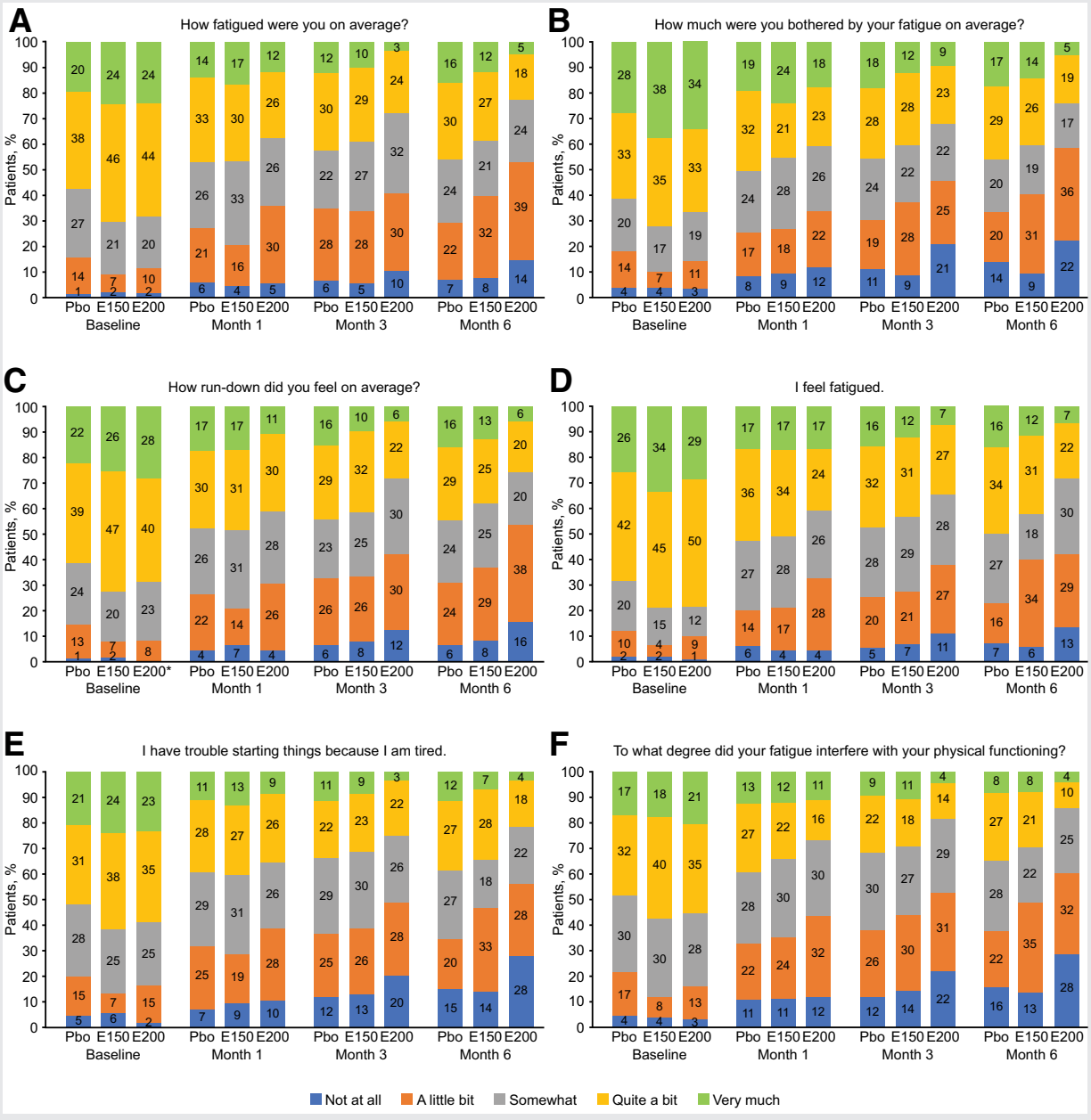
SUPPLEMENTAL FIGURE 1



Percentage of women reporting significant fatigue (defined as response of "quite a bit" or "very much") in PROMIS fatigue questions (modified intention-to-treat). N values (placebo/elagolix 150 mg QD/elagolix 200 mg BID): baseline: 371/246/243; month 1: 350/227/223; month 3: 316/219/202; month 6: 249/173/166. BID = twice daily; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily.

Surrey. Elagolix and fatigue reduction. Fertil Steril 2019.

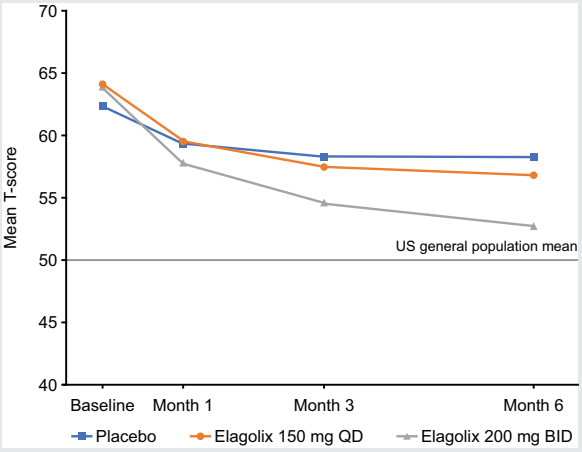
SUPPLEMENTAL FIGURE 2



Responses to PROMIS fatigue questions (modified intention-to-treat). N values (placebo [Pbo]/elagolix 150 mg QD [E150]/elagolix 200 mg BID [E200]): baseline: 371/246/243; month 1: 350/227/223; month 3: 316/219/202; month 6: 249/173/166. Value for "not at all" is 0. Abbreviations as in Supplemental Figure 1.

Surrey. Elagolix and fatigue reduction. Fertil Steril 2019.

SUPPLEMENTAL FIGURE 3



PROMIS Fatigue Questionnaire T-scores at months 1, 3, and 6 of treatment (modified intention-to-treat). N values (placebo/elagolix 150 QD/elagolix 200 BID): baseline: 371/246/243; month 1: 350/227/223; month 3: 316/219/202; month 6: 248/172/165. Abbreviations as in Supplemental Figure 1.

Surrey. Elagolix and fatigue reduction. Fertil Steril 2019.