ORIGINAL ARTICLE: ENDOMETRIOSIS

Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose–response manner: a randomized, double-blind, placebo-controlled study

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Objective: To evaluate the efficacy and safety of three dose levels of relugolix, a gonadotropin-releasing hormone receptor antagonist, compared with placebo and leuprorelin in women with endometriosis-associated pain.
Design: Phase 2, multicenter, randomized, double-blind, placebo-controlled study.
Setting: Hospitals and clinics.
Patient(s): Adult premenopausal women with endometriosis who had dysmenorrhea and endometriosis-associated pelvic pain.
Intervention(s): During a 12-week treatment period, patients received relugolix 10 mg (n = 103), 20 mg (n = 100), or 40 mg (n = 103) as a daily oral dose; placebo (n = 97) as a daily oral dose; or leuprorelin 3.75 mg (n = 80) as a monthly subcutaneous injection.
Main Outcome Measure(s): Primary endpoint was the change from baseline in mean visual analog scale score for pelvic pain during 28 days before the end of treatment.
Result(s): The mean changes in mean visual analog scale score for pelvic pain were −3.8 mm in the placebo group; −6.2, −8.1, and −10.4 mm in the relugolix 10-mg, 20-mg, and 40-mg groups; respectively; and −10.6 mm in the leuprorelin group. The major adverse events with relugolix were hot flush, metrorrhagia, menorrhagia, and irregular menstruation, and bone mineral density decrease in a dose–response manner, which were also observed in the leuprorelin group with a frequency comparable with that in the relugolix 40-mg group.
Conclusion(s): Oral administration of relugolix alleviated endometriosis-associated pain in a dose–response manner and was generally well tolerated. Relugolix 40 mg demonstrated efficacy and safety comparable with those of leuprorelin.
Clinical Trial Registration Number: NCT01458301. (Fertil Steril® 2020;■:■–■. ©2020 by American Society for Reproductive Medicine.)
Key Words: Endometriosis-associated pain, GnRH, gonadotropin-releasing hormone receptor antagonist, relugolix

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Endometriosis is a common benign estrogen-dependent chronic gynecological disorder characterized by the presence of endometrial tissue outside the endometrial cavity and is associated with pelvic pain, dysmenorrhea, dyspareunia, and infertility (1, 2). The prevalence of endometriosis is estimated to be 10% in women of reproductive age; furthermore, the frequency in women with pain, infertility, or both is estimated to be 35% to 50% (1). Current standard medications for endometriosis-associated pain include nonsteroidal anti-inflammatory drugs to treat pain, or combined oral contraceptives, progestogens, danazol, and gonadotropin-releasing hormone (GnRH) agonists as a hormonal approach (3). Combined oral contraceptive medications are not effective in all patients with endometriosis and are associated with increased risk for thromboembolic events (4). Progestin-only products provide effective relief from endometriosis-associated pain, similar to GnRH agonists and danazol, but may be associated with uterine bleeding (5). Injectable GnRH agonist peptides such as leuprorelin are effective for endometriosis-associated pain (4). However, GnRH agonists induce a transient increase in the secretion of gonadotropins, resulting in a temporary worsening of symptoms (6). Furthermore, it may take 3 to 4 weeks before therapeutic effects are observed.

Alternative therapeutic approaches to existing treatments are GnRH receptor antagonists, which are not associated with an initial clinical flare and typically have a better side-effect profile (6). Injectable GnRH antagonists may be used "off-label" in North America to treat endometriosis-associated pain (7). The oral GnRH receptor antagonist elagolix was recently approved by the U.S. Food and Drug Administration for treatment of pain associated with endometriosis (8).

Relugolix is an orally active, nonpeptide GnRH receptor antagonist that has a faster onset of action than GnRH agonists (9). Phase 1 studies in healthy premenopausal women demonstrated that multiple doses of $\leq$40 mg were generally well tolerated without dose-dependent safety trends of concern and showed rapid and sustained suppression of serum estradiol and progesterone levels (data on file, Takeda Pharmaceutical Company Limited, Tokyo, Japan). A phase 2 study of relugolix in women with heavy menstrual bleeding associated with uterine fibroids (UF) demonstrated reduction of menstrual bleeding and UF volume in a dose–response manner over 12 weeks of treatment compared with placebo (10). Based on these results, relugolix 40 mg was selected for further evaluation. In a phase 3 study in Japanese premenopausal women with heavy menstrual bleeding associated with UF, noninferiority of relugolix to leuprorelin in the improvement of heavy menstrual bleeding was confirmed (9). Another phase 3 study of relugolix in women with pain associated with UF demonstrated statistically significant improvement in pain symptoms compared with placebo (11). The safety profile of relugolix in those studies was generally well tolerated and reflected the low estrogen levels associated with the mechanism of action. Because of these data, relugolix 40 mg has been approved for the treatment of UF in Japan and is currently undergoing phase 3 clinical development in Japan for women with endometriosis. Relugolix is also under development for women's health indications globally (NCT03751124 and NCT03204331). This study evaluated the efficacy and safety of three dose levels of relugolix (10, 20, and 40 mg) orally administered once daily for 12 weeks in Japanese women with endometriosis-associated pain compared with placebo and a GnRH agonist, leuprorelin acetate (leuprorelin; 3.75 mg monthly injection), as an active reference treatment.

MATERIALS AND METHODS

Study Design

This phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study was conducted between December 2011 and September 2013 at 108 sites across Japan. The study was performed in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonization of Good Clinical Practice Guidelines, and all applicable laws and regulations. The protocol was reviewed and approved by institutional review boards in all the participating study sites. All patients provided written informed consent before enrollment in the study.

The study consisted of a pretreatment period of 4 to 12 weeks, during which patients underwent a double-dummy (relugolix and leuprorelin) placebo run-in period before randomization, a treatment period of 12 weeks, and a 4-week follow-up period after early discontinuation or completion of the treatment period. Patients who completed the 12-week treatment period could enter a 12-week extension study (total treatment period of 24 weeks) and had the 4-week follow-up period after completion of the extension.

During the pretreatment period, administration of the study drug (relugolix- and leuprorelin-placebos) to patients under single-blind conditions was initiated on days 1 to 5 of the first menstruation after informed consent was signed. After completion of the pretreatment period, eligible patients were randomly assigned to relugolix 10 mg, 20 mg, or 40 mg; placebo; or leuprorelin at a ratio of 2:2:2:2:1 according to a combination of computer-generated 5 $\times$ 5 and 4 $\times$ 4 Latin squares prepared by a patient registration center (Bell Medical Solutions, Inc., Tokyo, Japan). All randomization information was stored in a secured area, accessible only by authorized personnel. After randomization, administration of the study drug was initiated on days 1 to 5 of the second menstruation after informed consent was signed. All patients took one pill (relugolix 10, 20, or 40 mg or relugolix-placebo) once daily 30 minutes before breakfast and received a subcutaneous injection (leuprorelin 3.75 mg or leuprorelin-placebo) every 4 weeks for 12 weeks under double-blind conditions of patients and investigators. Sex hormone treatments were prohibited during the study. Analgesics were permitted at the discretion of the investigator to alleviate significant pain associated with endometriosis. Patients were instructed not to use analgesics for prophylactic purposes but to record their pain symptoms in a patient diary before taking analgesics.

Patients also recorded the following information in the patient diary on a daily basis from the pretreatment period to the end of treatment period: visual analog scale (VAS) assessments of pelvic pain, dysmenorrhea pain and

dyspareunia, presence or absence of menstruation and amount of bleeding (0 to 5 points scored by patients), study drug (relugolix) compliance, and use of analgesics. During the course of this study, patients visited the study site for planned evaluations every other week for the first month after the initiation of study drug administration, and monthly thereafter.

Patients

Eligible patients were Japanese premenopausal women, ≥20 years of age, who had regular menstrual cycles (25–38 days), a diagnosis of endometriosis in the previous 5 years (confirmed by laparotomy, laparoscopy, or magnetic resonance imaging detection of ovarian chocolate cyst[s]), and dysmenorrhea and pelvic pain due to endometriosis, either one or both of which were at least moderate as determined by the investigator using the Biberoglu and Behrman (B&B) scale (12). Exclusion criteria were measurable UF with the longest diameter ≥3 cm, lower abdominal pain due to irritable bowel syndrome or severe interstitial cystitis, thyroid dysfunction, pelvic inflammatory disease, a positive Papanicolaou smear test result, a history of hysterectomy or bilateral oophorectomy, and serious cardiovascular, hepatic, renal, or hematologic disorders.

Study Measures

Self-reported endometriosis-associated pain was measured by VAS by marking one point on the length of a 100-mm line providing a range of score from 0 (absence of pain) to 100 mm (unbearable pain). VAS scores were measured daily from the time informed consent was obtained to the end of the treatment period. The primary endpoint was the change from baseline in mean VAS score for pelvic pain during the 28 days before the end of the treatment period. Baseline VAS score was defined as the mean VAS score during the pretreatment placebo run-in period. Secondary endpoints included the change from baseline in VAS scores for pelvic pain and dyspareunia during the treatment period. Safety endpoints included treatment-emergent adverse events (TEAEs), bone mineral density (BMD) assessed by dual-energy x-ray absorptiometry, vital signs, changes in body weight, 12-lead electrocardiogram, and clinical laboratory test results. Additional endpoints included modified B&B (M-B&B) score reported by each patient to evaluate pain symptoms such as pelvic pain during dysmenorrhea and deep dyspareunia and B&B score reported by the investigator through interviews with the patient to evaluate pain symptoms such as dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration (12). Analgesic use during the treatment period, quality of life assessed by patients using the Endometriosis Health Profile-30 (EHP-30) (13, 14), and serum concentrations of estradiol, luteinizing hormone (LH), follicle-stimulating hormone, and progesterone were also measured. A central laboratory (SRL Medisearch Inc.) performed laboratory tests for serum chemistry, hematology, urinalysis, and pharmacodynamics. Each investigational site conducted urine pregnancy tests.

Statistical Analyses

On the basis of previous clinical studies that compared dienogest and leuprorelin for the treatment of endometriosis-associated pain (15, 16), the difference in changes from baseline in mean VAS score during the 28 days before the end of the treatment period between the relugolix groups and the placebo group was assumed to be −12 mm (standard deviation 30 mm). Based on these assumptions, 100 patients per group were needed to achieve a power of at least 80% to detect the difference between treatment groups by two-sample *t* test at a significance level of 5% (two-sided). Taken together with the assumption that approximately 10% of randomized patients would be excluded from the analysis of the primary endpoint, 110 patients were to be randomized to each relugolix group and the placebo group. Fifty-five patients were to be randomized to the leuprorelin group as a reference treatment.

Efficacy analyses were performed on the full analysis set, defined as all patients who were randomized and received at least one dose of the study drug. For the primary endpoint, summary statistics and the two-sided 95% confidence interval (CI) of the mean were calculated. The point estimate and two-sided 95% CI of the difference in the adjusted mean between each relugolix group and the placebo group were calculated based on an analysis of covariance model using the primary endpoint as a response, the mean VAS score at baseline as a covariate, and treatment group as a factor. Comparisons between the relugolix treatment and placebo groups (starting with the 40-mg dose) were also performed using the closed testing procedure to control overall type 1 error rate at two-sided 5% significance level. A P value $<.05$ was considered statistically significant. For secondary endpoints, analyses similar to the primary endpoint were performed on the change in the mean VAS score at each measurement time point using the full analysis set. All the statistical analyses were performed with SAS version 9.2 (SAS Institute Japan Ltd.).

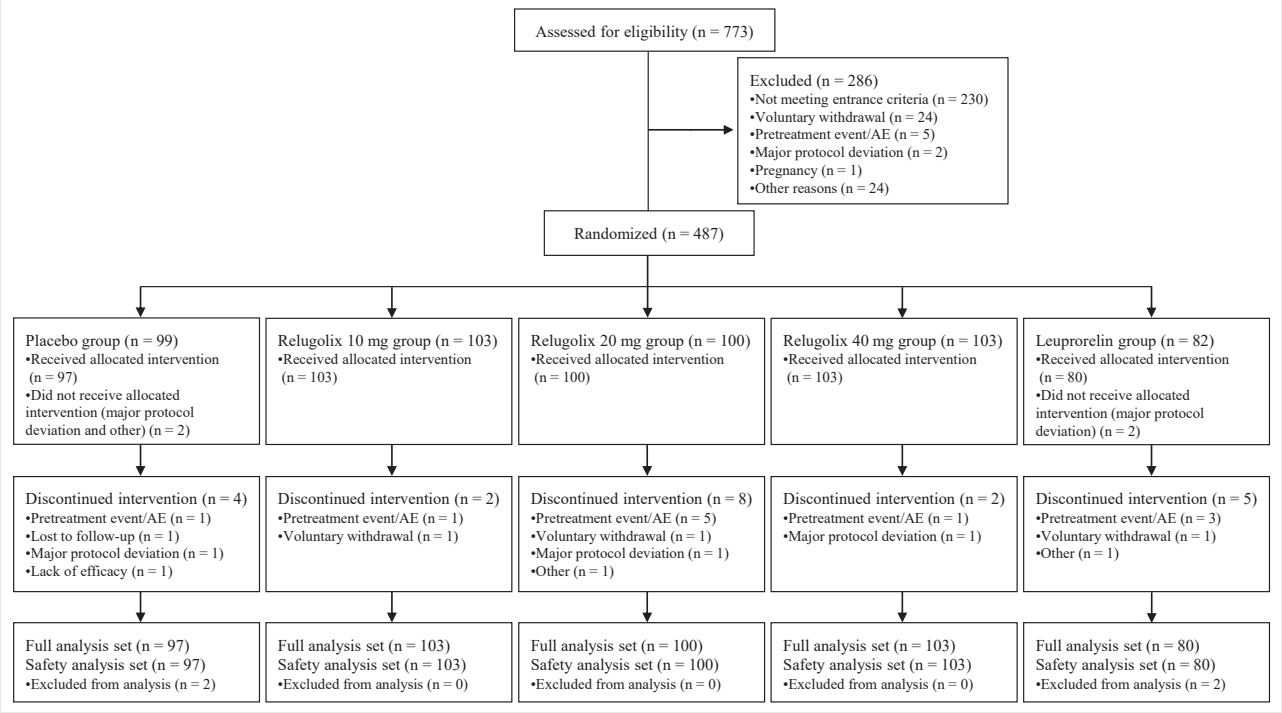
Safety analyses were performed on the safety analysis set, defined as all patients who received at least one dose of the study medication. TEAEs were coded by use of the Medical Dictionary for Regulatory Activities version 16.1. For continuous variables (including BMD, vital signs, body weight, clinical laboratory tests, and electrocardiogram), baseline values, observed values, and changes from baseline were summarized for each measurement time point.

RESULTS

Study Population

A total of 487 patients, aged between 20 and 50 years, were randomized to placebo (n = 99), relugolix 10 mg (n = 103), relugolix 20 mg (n = 100), relugolix 40 mg (n = 103), and leuprorelin (n = 82) (Fig. 1). Although a 2:2:2:2:1 randomization ratio between placebo; relugolix 10 mg, 20 mg, and 40 mg; and leuprorelin was planned, the actual percentage of subjects assigned to the leuprorelin group was higher than planned because the randomization scheme consisted of a combination of 5 × 5 and 4 × 4 Latin squares, such that at least one subject was assigned to each of five groups if an investigational site enrolled five or more subjects. Four of

FIGURE 1



Patient disposition flow chart.

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the randomized patients were not administered study drug; the reasons were "major protocol deviation" (one subject in the placebo group and two subjects in the leuprorelin group) and "other" (for one subject who was administered commercial leuprorelin acetate in the placebo group). The mean VAS scores at baseline across treatment groups for pelvic pain ranged from 14.6 to 15.6 mm, for dysmenorrhea ranged from 27.1 to 30.4 mm, and for dyspareunia from 8.8 to 12.5 mm. Overall, the treatment groups were similar in demographic and baseline characteristics (Table 1).

Efficacy Assessments

In the primary endpoint, the mean (95% CI) changes from baseline in mean VAS score for pelvic pain during the 28 days before the end of the treatment period were −3.8 (−5.9, −1.6) mm in the placebo group, −6.2 (−8.0, −4.4), −8.1 (−10.7, −5.4), and −10.4 (−12.6, −8.3) mm in the relugolix 10-mg, 20-mg, and 40-mg groups, respectively, and −10.6 (−12.9, −8.3) mm in the leuprorelin group. A statistically significant difference between each relugolix group and placebo group was observed ($P<.05$), with a P value of $<.0001$ for the relugolix 40-mg group vs. placebo (Fig. 2A). The difference (95% CI) between the relugolix and placebo groups were −2.9 (−5.3, −0.5) mm for the relugolix 10-mg group, −4.3 (−6.8, −1.9) mm for the relugolix 20-mg group, and −6.8 (−9.2, −4.4) mm for the relugolix 40-mg group. In the secondary endpoint, the mean VAS score for pelvic pain during the treatment period in the relugolix groups started to decrease within the first month of treatment in a dose–response manner and continued throughout the treatment period (Fig. 2B). Similar results were observed for dysmenorrhea pain (Fig. 2C). However, the results for dyspareunia showed no clear trend of changes in relugolix (Fig. 2D). The mean VAS scores for pelvic pain and dysmenorrhea pain in the relugolix 40-mg group were comparable with those in the leuprorelin group (Fig. 2B and 2C).

Regarding the additional endpoints, similar results to efficacy of relugolix in VAS score were observed in other indexes for pain symptoms, M-B&B score, and B&B score (Supplemental Tables 1 and 2, available online). The frequency of analgesic use tended to decrease with increasing relugolix dose at the end of treatment. In quality-of-life evaluations, the EHP-30 scores generally improved in relugolix-treated patients compared with placebo-treated patients at week 12 (Supplemental Table 3, available online).

As for GnRH-related hormone release, serum estradiol, LH, follicle-stimulating hormone, and progesterone levels in the relugolix groups decreased generally in a dose–response manner, and those serum hormone levels in the leuprorelin group decreased to levels comparable with those in the relugolix 40-mg group (Supplemental Fig. 1, available online). Notably, the serum estradiol and LH levels decreased more rapidly after the initiation of treatment in the relugolix 40-mg group than in the leuprorelin group and remained at the low levels until the end of treatment.

TABLE 1

Demographic and baseline characteristics.

Characteristic	Relugolix 10 mg (n = 103)	Relugolix 20 mg (n = 100)	Relugolix 40 mg (n = 103)	Leuprorelin 3.75 mg (n = 82)	Placebo (n = 99)
Age (y)	35.3 (6.2)	35.1 (6.8)	35.6 (6.0)	36.1 (6.1)	35.7 (6.1)
BMI, kg/m^2	103	100	103	81	97
	21.5 (3.3)	20.4 (2.5)	21.6 (3.1)	21.8 (3.4)	21.1 (3.0)
Disease duration (y)	3.8 (5.0)	3.2 (3.8)	4.3 (5.5)	2.9 (3.8)	3.9 (4.7)
VAS score, mm					
Pelvic pain	103	100	103	81	97
	14.6 (12.0)	15.6 (15.1)	15.3 (12.0)	15.2 (15.1)	15.6 (14.3)
Dysmenorrhea	103	100	103	81	97
	28.2 (17.6)	27.7 (18.9)	30.4 (17.0)	27.1 (19. 8)	28.4 (16.6)
Dyspareunia	46	47	44	26	41
	8.8 (14.2)	12.5 (16.5)	9.4 (15.4)	9.5 (10.7)	11.0 (14.2)
M-B&B score					
Pelvic pain	103	100	103	81	97
	0.66 (0.46)	0.63 (0.47)	0.65 (0.44)	0.68 (0.55)	0.65 (0.45)
Dysmenorrhea	103	100	103	81	97
	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.2 (0.4)
Deep dyspareunia	46	47	44	26	41
	0.56 (0.60)	0.64 (0.55)	0.55 (0.48)	0.60 (0.45)	0.55 (0.45)
EHP-30 score	103	100	103	81	97
Pain	28.6 (21.8)	26.7 (18.6)	28.9 (20.1)	26.5 (19.6)	24.8 (20.0)
Control and powerlessness	27.4 (23.0)	28.6 (22.5)	25.9 (21.2)	27.8 (22.9)	25.8 (20.8)
Emotional well-being	21.8 (20.1)	23.8 (19.3)	20.4 (17.5)	21.2 (19.1)	23.0 (20.0)
Social support	16.5 (17.7)	20.0 (20.6)	15.7 (18.7)	17.1 (20.3)	17.7 (20.0)
Self-image	15.9 (16.7)	15.7 (18.1)	15.0 (18.7)	16.3 (21.9)	19.4 (22.2)
Proportion of days with analgesic use (%)	103	100	103	81	97
	12.5 (12.3)	13.3 (16.4)	12.0 (14.5)	11.6 (13.8)	10.0 (11.5)
Amount score of bleeding	103	100	103	81	97
	2.3 (0.5)	2.3 (0.6)	2.4 (0.5)	2.4 (0.6)	2.3 (0.5)

Note: Data presented as mean (standard deviation) or n, unless stated otherwise. BMI = body mass index; EHP-30 = Endometriosis Health Profile-30; M-B&B score = Modified Biberoglu and Behrman score; VAS = visual analog scale.

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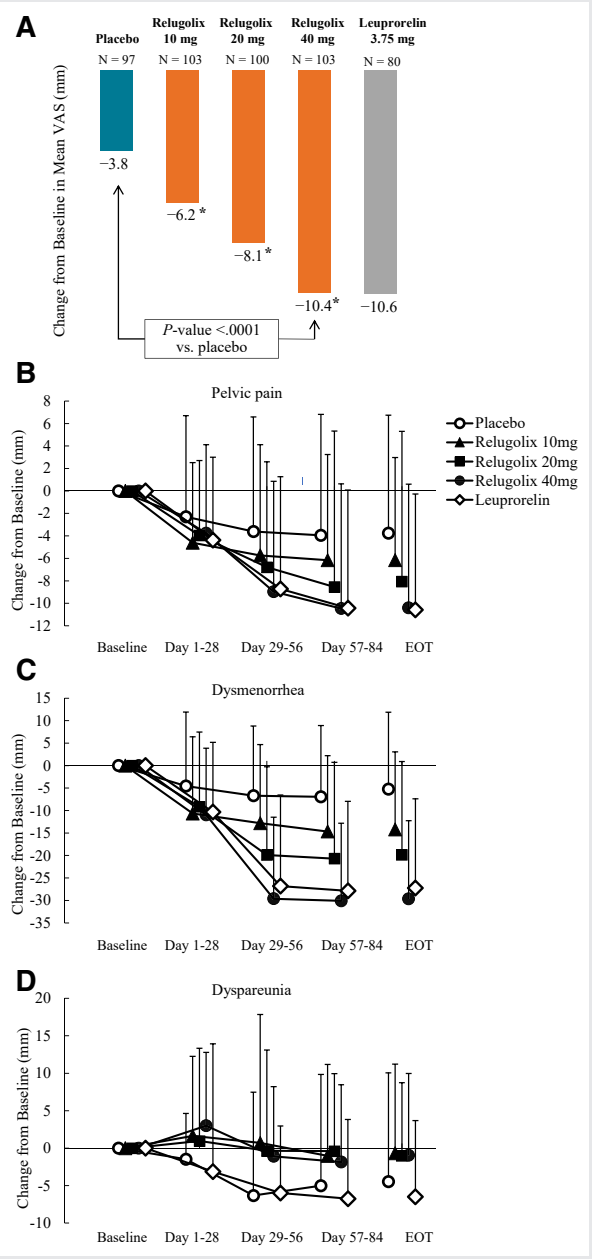
Safety Assessments

The incidence of TEAEs was 71.1% in the placebo group; 79.6%, 89.0%, and 94.2% in the relugolix 10-mg, 20-mg, and 40-mg groups, respectively; and 91.3% in the leuprorelin group (Table 2). TEAEs with an incidence of ≥10% in the relugolix groups were nasopharyngitis, headache, metrorrhagia, menorrhagia, irregular menstruation, hyperhidrosis, and hot flush. Of those, the incidences of metrorrhagia, irregular menstruation, and hot flush were ≥10% higher in either the relugolix or the leuprorelin groups, or both, than in the placebo group. The intensity of TEAEs was mild or moderate except for one severe TEAE (increased blood creatine phosphokinase) in the placebo group.

No deaths occurred during this study. Four serious TEAEs occurred in four patients. Three of them were not considered to be related to the study drug in the placebo group. The remaining one serious TEAE was abnormal liver function test results considered to be related to the study drug in the relugolix 20-mg group. This patient was a 37-year-old woman with endometriosis, a medical history of Sjogren's syndrome, and concomitant medications including acetaminophen and celecoxib. She experienced fever on study day 49 and testing for a viral cause gave negative results. An acetaminophen level was not obtained. The elevated liver function test results (alanine aminotransferase 1,268 IU/L and aspartate aminotransferase 1,189 IU/L without elevated bilirubin) resolved after relugolix, acetaminophen, and celecoxib were discontinued. TEAEs leading to discontinuation of the study drug were observed in one patient in the placebo group (ovarian cyst ruptured), one patient in the relugolix 10-mg group (hot flush), five patients in the relugolix 20-mg group (hemorrhagic ovarian cyst, abnormal liver function test result, hot flush/hyperhidrosis, menopausal symptoms, and injection site swelling), one patient in the relugolix 40-mg group (drug eruption [an adverse drug reaction of the skin]), and three patients in the leuprorelin group (hot flush and dizziness; irritability, musculoskeletal stiffness, malaise, headache, mental impairment, and flat affect; and menorrhagia).

The mean percentage changes (standard devation) in BMD from baseline were −0.1% (1.7) in the placebo group, −1.0% (1.9) in the relugolix 10-mg group, −1.3% (2.1) in the relugolix 20-mg group, −2.1% (2.2) in the relugolix 40-mg group, and −2.2% (1.7) in the leuprorelin group, indicating that treatment of relugolix decreased BMD in a dose–response manner and that the effects on BMD were comparable between the relugolix 40-mg and leuprorelin groups over the short duration of the study (12 weeks). There were no

FIGURE 2



(**A**) Mean change from baseline in the visual analog scale score for pelvic pain for 28 days before the end of treatment period. (**B**) Mean (standard deviation) changes from baseline in the visual analog scale score for (**B**) pelvic pain, (**C**) dysmenorrhea, and (**D**) dyspareunia. EOT = end of treatment period; VAS = visual analog scale. *$P<.05$ vs. placebo.

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clinically significant changes in vital signs, body weight, electrocardiogram, and laboratory values in any treatment groups.

DISCUSSION

Relugolix at doses of 10 mg, 20 mg, and 40 mg demonstrated superiority of therapeutic efficacy on pelvic pain compared with placebo, and relugolix at a dose of 40 mg had efficacy comparable with that of leuprorelin. Similarly, dysmenorrhea was improved by relugolix in a dose–response manner, where the therapeutic effect on dysmenorrhea in the relugolix 40-mg group was also comparable with that in the leuprorelin group. However, no clear trend in changes in dyspareunia was observed for relugolix. This may be because the sample size was too small to detect any differences. Pain evaluation in dyspareunia was measured only in patients who engaged in intercourse during the study period, and some patients with dyspareunia possibly avoided sexual intercourse.

The efficacy of relugolix for endometriosis-associated pain according to the VAS score was supported by the results using other indexes for pain evaluation, the M-B&B and B&B scores. Moreover, the lower frequency of analgesic use in the relugolix group and the leuprorelin group may also have resulted from the efficacy of relugolix and leuprorelin on endometriosis-associated pain. Reduced or stable analgesic use and decreases in endometriosis-related pain have also been demonstrated for elagolix (17), another oral GnRH antagonist, although direct comparisons of efficacy between studies are difficult owing to differences in the pain rating scales used. Other endometriosis-related symptoms including amount score of menstrual bleeding and "pain" and "control and powerlessness" based on EHP-30 were also improved by relugolix in a dose–response manner, suggesting that relugolix should improve not only endometriosis-associated pain but also other endometriosis-related symptoms.

Although numerous classes of medical therapies are currently used for the treatment of endometriosis-related pain (3–7), they have inherent limitations, including limited efficacy in treating endometriosis (nonsteroidal anti-inflammatory drugs) (3, 4), the risk of adverse events (e.g., danazol, combined oral contraceptives, progestins) (3–5, 7), and their tolerability in long-term treatment (e.g., GnRH agonists) (3, 4, 7). The oral GnRH antagonists relugolix and elagolix offer benefits that overcome some of those limitations, including easier administration and dose adjustment than their injectable counterparts. Given their demonstrated efficacy in reducing endometriosis-related pain (17), oral agents such as relugolix may be a new therapeutic treatment option for patients with endometriosis. In addition to the oral GnRH antagonists, several injectable agents (e.g., cetrorelix, ganirelix, and degarelix) are under investigation; however, they have yet to be investigated in randomized controlled trials, and their benefits in reducing endometriosis-related symptoms or pain remain to be elucidated.

Analysis of pharmacodynamic parameters showed that the median serum estradiol concentration in the relugolix 40-mg group reached the lower limit of quantitation at week 2 after the start of treatment, whereas 4 weeks were required to reach the same level in the leuprorelin group. This discrepancy is likely a result of increased secretion of gonadotropins from the GnRH agonist leuprorelin and a resulting transient increase in estradiol concentration on leuprorelin administration. Relugolix instead antagonizes GnRH through the GnRH receptors, resulting in decreased estradiol from the early stage of the treatment period.

TABLE 2

Summary of treatment-emergent adverse events.

Variable	Relugolix 10 mg (n = 103)	Relugolix 20 mg (n = 100)	Relugolix 40 mg (n = 103)	Leuprorelin 3.75 mg (n = 80)	Placebo (n = 97)
TEAEs	205	232	280	238	165
Patients with any TEAEs	82 (79.6)	89 (89.0)	97 (94.2)	73 (91.3)	69 (71.1)
Patients with drug-related TEAEs	64 (62.1)	82 (82.0)	88 (85.4)	67 (83.8)	36 (37.1)
Intensity of TEAEs					
Mild	78 (75.7)	80 (80.0)	88 (85.4)	63 (78.8)	63 (64.9)
Moderate	4 (3.9)	9 (9.0)	9 (8.7)	10 (12.5)	5 (5.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
TEAEs leading to study drug discontinuation	1 (1.0)	5 (5.0)	1 (1.0)	3 (3.8)	1 (1.0)
Serious TEAEs	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	3 (3.1)
TEAEs occurring in ≥10% of patients in any treatment group					
Nasopharyngitis	21 (20.4)	19 (19.0)	22 (21.4)	15 (18.8)	21 (21.6)
Headache	4 (3.9)	11 (11.0)	6 (5.8)	8 (10.0)	9 (9.3)
Metrorrhagia	26 (25.2)	30 (30.0)	25 (24.3)	32 (40.0)	4 (4.1)
Menorrhagia	7 (6.8)	14 (14.0)	13 (12.6)	9 (11.3)	4 (4.1)
Irregular menstruation	16 (15.5)	19 (19.0)	3 (2.9)	5 (6.3)	4 (4.1)
Genital hemorrhage	3 (2.9)	4 (4.0)	5 (4.9)	8 (10.0)	1 (1.0)
Hyperhidrosis	3 (2.9)	10 (10.0)	10 (9.7)	7 (8.8)	1 (1.0)
Hot flush	9 (8.7)	19 (19.0)	54 (52.4)	33 (41.3)	8 (8.2)

Note: Data present as n or n (%), unless stated otherwise. TEAE = treatment-emergent adverse event.

Osuga. Relugolix for endometriosis pain. Fertil Steril 2020.

The incidence of TEAEs was greater with higher doses of relugolix, and TEAEs were more frequent in the relugolix 20-mg and 40-mg groups than in the placebo group. However, there were no clinically significant or unexpected TEAEs related to the study drug. The most common TEAEs with relugolix included hot flush, metrorrhagia, menorrhagia, and irregular menstruation. A decrease in BMD was observed in a dose–response manner. These TEAEs were considered to be due to the estrogen-lowering effect of relugolix and were also observed in the leuprorelin group with similar frequency. The timing of the incidence of hot flush demonstrates the differences between the mechanisms of action of the GnRH antagonist relugolix and the GnRH agonist leuprorelin. About half of the reported hot flush in the relugolix 20-mg and 40-mg groups was observed during days 1 to 28, whereas that in the leuprorelin group was reported mainly during days 29 to 56. It may be possible to mitigate the estrogen deprivation side effects through the combined use of low-dose hormones, balancing the benefits of symptom reduction and the risks of bone loss and vasomotor symptoms. This approach is under investigation in the ongoing global phase 3 SPIRIT studies in women with pain associated with endometriosis (NCT03654274, NCT03204318, NCT03204331).

This study had some limitations. First, we assessed the efficacy and safety of relugolix for only ≤12 weeks, which is short for investigating the possibility of long-term use. Possible improvements in some quality-of-life outcomes may not have been apparent by 12 weeks. Second, because we included only Japanese patients, generalizability of the results may be difficult without additional data. Third, limitations for interpreting the dyspareunia data include both the small sample size and the small number of patients who had sexual intercourse during the study.

In conclusion, 12-week treatment with relugolix up to 40 mg significantly improved endometriosis-associated pain in a dose–response manner and was generally well tolerated, with a safety profile consistent with its mechanism of action. Relugolix 40 mg showed efficacy comparable with that of leuprorelin without inducing clinical flare. Hence, relugolix may become a new therapeutic option for patients with endometriosis-associated pain. The 40-mg dose of relugolix is being evaluated further in phase 3 studies for the treatment of patients with endometriosis.

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