Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomised, double-blind, studies (SPIRIT 1 and 2)

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Summary

Background Endometriosis is a common cause of pelvic pain in women, for which current treatment options are suboptimal. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, combined with estradiol and a progestin, was evaluated for treatment of endometriosis-associated pain.

Methods In these two replicate, phase 3, multicentre, randomised, double-blind, placebo-controlled trials at 219 community and hospital research centres in Africa, Australasia, Europe, North America, and South America, we randomly assigned women aged 18–50 years with surgically or directly visualised endometriosis with or without histological confirmation, or with histological diagnosis alone. Participants were eligible if they had moderate to severe endometriosis-associated pain and, during the 35-day run-in period, a dysmenorrhoea Numerical Rating Scale (NRS) score of 4·0 or higher on two or more days and a mean non-menstrual pelvic pain NRS score of 2·5 or higher, or a mean score of 1·25 or higher that included a score of 5 or more on 4 or more days. Women received (1:1:1) once-daily oral placebo, relugolix combination therapy (relugolix 40 mg, estradiol 1 mg, norethisterone acetate 0·5 mg), or delayed relugolix combination therapy (relugolix 40 mg monotherapy followed by relugolix combination therapy, each for 12 weeks) for 24 weeks. During the double-blind randomised treatment and follow-up period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study were masked to treatment assignment. The co-primary endpoints were responder rates at week 24 for dysmenorrhoea and non-menstrual pelvic pain, both based on NRS scores and analgesic use. Efficacy and safety were analysed in the modified intent-to-treat population (randomised patients who received ≥1 study drug dose). The studies are registered at ClinicalTrials.gov (SPIRIT 1 [NCT03204318] and SPIRIT 2 [NCT03204331]) and EudraCT (SPIRIT 1 [2017–001588–19] and SPIRIT 2 [2017–001632–19]). Eligible patients who completed the SPIRIT studies could enrol in a currently ongoing 80-week open-label extension study (SPIRIT EXTENSION [NCT03654274, EudraCT 2017-004066-10]). Database lock for the on-treatment duration has occurred, and post-treatment follow-up for safety, specificially for bone mineral density and menses recovery, is ongoing at the time of publication.

Findings 638 patients were enrolled into SPIRIT 1 and randomly assigned between Dec 7, 2017, and Dec 4, 2019, to receive relugolix combination therapy (212 [33%]), placebo (213 [33%]), or relugolix delayed combination therapy (213 [33%]). 623 patients were enrolled into SPIRIT 2 and were randomly assigned between Nov 1, 2017 and Oct 4, 2019, to receive relugolix combination therapy (208 [33%]), placebo (208 [33%]), or relugolix delayed combination therapy (207 [33%]). 98 (15%) patients terminated study participation early in SPIRIT 1 and 115 (18%) in SPIRIT 2. In SPIRIT 1, 158 (75%) of 212 patients in the relugolix combination therapy group met the dysmenorrhoea responder criteria compared with 57 (27%) of 212 patients in the placebo group (treatment difference 47·6% [95% CI 39·3–56·0]; p<0·0001). In SPIRIT 2, 155 (75%) of 206 patients in the relugolix combination therapy group were dysmenorrhoea responders compared with 62 (30%) of 204 patients in the placebo group (treatment difference 44·9% [95% CI 36·2–53·5]; p<0·0001). In SPIRIT 1, 124 (58%) of 212 patients in the relugolix combination therapy group met the non-menstrual pelvic pain responder criteria versus 84 (40%) patients in the placebo group (treatment difference 18·9% [9·5–28·2]; p<0·0001). In SPIRIT 2, 136 (66%) of 206 patients were non-menstrual pelvic pain responders in the relugolix combination therapy group compared with 87 (43%) of 204 patients in the placebo group (treatment difference 23·4% [95% CI 13·9–32·8]; p<0·0001). The most common adverse events were headache, nasopharyngitis, and hot flushes. There were nine reports of suicidal ideation across both studies (two in the placebo run-in, two in the placebo group, two in the relugolix combination therapy group, and three in the delayed relugolix combination therapy group). No deaths were reported. Least squares mean percentage change in lumbar spine bone mineral density in the relugolix combination therapy versus placebo groups was –0·70% versus 0·21% in SPIRIT 1 and –0·78% versus 0·02% in SPIRIT 2, and in the delayed relugolix combination group was –2·0% in SPIRIT 1 and –1·9% in SPIRIT 2. Decreases in opioid use were seen in treated patients as compared with placebo.

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Interpretation Once-daily relugolix combination therapy significantly improved endometriosis-associated pain and was well tolerated. This oral therapy has the potential to address the unmet clinical need for long-term medical treatment for endometriosis, reducing the need for opioid use or repeated surgical treatment.

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Introduction

Endometriosis, a chronic inflammatory disease characterised by lesions of endometrial-like tissue outside the uterus, is associated with pelvic pain and infertility and affects 10% of women in their reproductive years.[1–3] Proliferation of endometriotic lesions requires oestradiol, which is proinflammatory,[1] and guidelines recommend long-term treatment of endometriosis to inhibit ovulation or reduce oestrogen production.[1,2,4,5]

The clinical course in endometriosis can be challenging for the patient. Independent of treatment approach, whether medical or surgical, 50% of patients typically have recurrence of symptoms over 5 years.[1] Given that current medical treatments and surgical interventions might offer incomplete pain relief, patients rely on opioid use to control pain as well as repeated surgeries.[6,7] Hormonal contraceptives or progestins are mainstays of treatment.[1] Gonadotropin-releasing hormone (GnRH) agonist therapy, associated with profound oestradiol suppression, is used as second-line treatment because hypoestrogenic side-effects and diminished bone density limit duration of use or require additional concomitant hormonal administration.[1–3] The oral GnRH antagonist, elagolix, reduces moderate-to-severe endometriosis-associated pain and is approved in the USA as a once-daily low dose or a more effective twice-daily high dose.[8] However, hypoestrogenic-induced declines in bone mineral density mean that elagolix treatment duration is a maximum of 24 months

Research in context

Evidence before this study

The design of SPIRIT 1 and SPIRIT 2 was based on evidence obtained from the clinical development of relugolix, including preclinical studies, phase 1 single dose and multi-dose pharmacokinetic and pharmacodynamic studies, and a phase 2 dose-ranging trial. We searched PubMed and Embase for all Article types using search terms, "endometriosis" + "treatment" + "phase" [all fields]; "relugolix", "leuprolide", "elagolix", + "endometriosis" [all fields]) with no restrictions on date or study duration. Non-English studies were excluded. Although GnRH receptor agonists and an antagonist are approved for the treatment of endometriosis-associated pain, they are administered as monotherapy, with the exception of leuprolide acetate for depot suspension, which is available co-packaged with norethisterone acetate tablet. These treatment options have either suboptimal efficacy at low doses, require injections, or are associated with undesirable hypoestrogenic adverse effects of hot flushes and bone density loss at high doses. In a phase 2 dose-ranging study in women with endometriosis-associated pain, 24-week treatment with relugolix 40 mg monotherapy was associated with significant reduction in pelvic pain versus placebo, with efficacy similar to leuprolide. However, dose-dependent decreases in bone mineral density and increases in vasomotor symptoms limited the duration of use. *Relugolix combination therapy* (consisting of 40 relugolix, 1 mg estradiol, and 0·5 mg norethisterone acetate) was developed as a once-daily treatment to achieve efficacy and minimise vasomotor symptoms and bone mineral density loss by maintaining oestradiol concentrations within a therapeutic range consistent with those in the early follicular phase of the menstrual cycle.

Added value of this study

Two large replicate pivotal phase 3 randomised, double-blind studies evaluated the combination of relugolix, estradiol, and norethisterone acetate compared with placebo in women with substantial endometriosis-associated pain, including dysmenorrhoea and non-menstrual pelvic pain. Demographic and baseline characteristics in these studies reflected high baseline pain intensity, substantial physical limitations, and high analgesic use as evidence of a substantial effect of disease on these women. Treatment with relugolix combination therapy for 24 weeks was associated with a significantly greater treatment response for the co-primary endpoints of dysmenorrhoea and non-menstrual pain compared with placebo. The improvement of endometriosis-associated pain, improvement in function, and reduction of the need for opioid use with a treatment that was well tolerated helps address the need for a long-term treatment solution by counteracting signs and symptoms associated with a hypoestrogenic state.

Implications of all the available evidence

The SPIRIT replicate trials showed that relugolix combination therapy, an oral GnRH receptor antagonist combined with estradiol and norethisterone acetate, administered as a once-daily dosing regimen, reduced endometriosis-associated pain from moderate and severe levels to minimal levels, improved pain-associated functionality, and minimised hypoestrogenic effects with low rates of hot flushes and bone density loss of less than 1%. The long-term therapeutic effects are being further assessed in an 80-week long-term extension study, which will provide up to 2 years of benefit and risk information for relugolix combination therapy.

for a low dose (6 months in patients with moderate hepatic impairment) and 6 months for a high-dose regimen.[9] Thus, there remains an important clinical need for safe and highly effective medical treatments that can be used conveniently and long term for endometriosis-related pain. The ability of such treatments to reduce the need for opioids and repeated surgery are additional clinically relevant and desirable attributes.

Relugolix is an oral non-peptide GnRH receptor antagonist. It competitively binds to pituitary GnRH receptors, blocking binding of endogenous GnRH with reversible, dose-dependent suppression of luteinising hormone and follicle-stimulating hormone,[10] and ovarian oestradiol and progesterone production.[11] In a phase 2 dose-ranging study in women with endometriosis-associated pain, treatment with 40 mg relugolix monotherapy daily for 24 weeks was associated with significant reduction in pelvic pain compared with placebo, with efficacy similar to leuprolide.[12] However, dose-dependent decreases in bone mineral density and increases in vasomotor symptoms mean that monotherapy relugolix is not suitable for long-term use.

Relugolix combination therapy (40 mg relugolix, 1 mg estradiol, and 0·5 mg norethisterone acetate) was developed as a once-daily treatment for uterine fibroids or endometriosis to achieve efficacy and minimise vasomotor symptoms and bone mineral density loss by maintaining oestradiol concentrations within a therapeutic range consistent with those in the early follicular phase of the menstrual cycle.[13,14] Relugolix combination therapy is approved for treatment of uterine fibroids in the EU and the USA.[15,16] Herein, we report the efficacy and safety of 24-week, once-daily oral relugolix combination therapy in women with endometriosis-associated pain.

Methods

Study design and patients

SPIRIT 1 and SPIRIT 2 are two replicate, phase 3, multicentre, randomised, double-blind, placebo-controlled studies that were done at 219 community and hospital research centres in Africa, Australasia, Europe, North America, and South America (appendix pp 2–8). We decided to do two replicate studies to establish effectiveness by showing reproducibility of the findings, as is required for regulatory purposes.[17] Four centres in the USA and five centres in Poland were included in both studies; apart from these, all centres were included in only one study. Premenopausal women aged 18–50 years with endometriosis that was surgically or directly visualised with or without histological confirmation, or histological diagnosis alone, within the past 10 years were eligible to participate. Patients who self reported moderate, severe, or very severe dysmenorrhea during their most recent menses, and moderate, severe, or very severe non-menstrual pelvic pain during the past month using the Endometriosis Associated Pain Severity score, could enter the run-in period. To be eligible for randomisation, patients were required to have a dysmenorrhea Numerical Rating Scale (NRS; 0=no pain; 10=pain as bad as you can imagine) score of 4·0 or higher for at least 2 days during the run-in period together with a mean non-menstrual pelvic pain score of at least 2·5, or a mean non-menstrual pain score of 1·25 with a score of at least 5·0 on 4 or more days.[18] Participants were required to have menstruated for at least 3 days during the run-in period. Non-hormonal contraception was required during study participation. Past medical history, including self-reported psychiatry history, and concomitant medications were recorded at baseline. Among the exclusion criteria were a bone mineral density by dual energy x-ray absorptiometry Z score of less than –2·0 at the lumbar spine, total hip, or femoral neck; history of chronic pelvic pain not caused by endometriosis; or having a contraindication to use of combined hormonal therapy. The full list of eligibility criteria is provided in the appendix (p 25). All patients provided written informed consent. The protocols were approved by local institutional review boards, and the studies were done in accordance with the International Conference on Harmonisation guidelines and ethical principles of the Declaration of Helsinki.

Randomisation and masking

Eligible women were randomised 1:1:1 to placebo, relugolix combination therapy, or delayed relugolix combination therapy. The delayed relugolix combination therapy group was included to compare bone mineral density and vasomotor symptoms for relugolix monotherapy with relugolix combination therapy at week 12. A permuted block randomisation was used for each study with a block size of six. Randomisation was stratified by geographical region (North America *vs* all other regions) and time since surgical endometriosis diagnosis (<5 years or ≥5 years) to ensure a balanced number of patients across treatment groups for assessment of effect.

Assignment to treatment group was determined by the Interactive Voice/Web Recognition Service (IVRS/IWRS) during the patient's baseline day 1 visit after confirmation that the patient met all eligibility criteria. During the single-blind run-in period, only patients were masked to treatment group. During the double-blind randomised treatment and follow-up period, all patients, investigators, and sponsor staff or representatives involved in the conduct of the study were masked to treatment assignment. Unmasked parties, none of whom were engaged in the conduct of the study, included the statisticians responsible for developing the randomisation codes, the Data Monitoring Committee and supporting statistical group, and staff managing drug supply, safety services (for individual patients only in connection with regulatory reporting of safety cases), and the IVRS/IWRS system.

See Online for appendix

Procedures

At screening, women who self-reported moderate, severe, or very severe dysmenorrhoea during their most recent

menses, and moderate or severe non-menstrual pelvic pain during the past month as determined by the Endometriosis Associated Pain Severity score, could enrol into the single-blind run-in period, during which they received placebo and prespecified rescue analgesic medications for symptomatic management; the purpose of this period was to avoid the randomisation of patients who exhibited a robust placebo response or sufficient placebo response that resulted in them not meeting the minimum threshold for pain severity. Patients who met the threshold of NRS pain scores during the approximately 35-day run-in period were randomly assigned to placebo, relugolix combination therapy (once-daily relugolix 40 mg orally as a tablet and estradiol 1 mg and norethisterone acetate 0·5 mg orally as a capsule), or delayed relugolix combination therapy (relugolix 40 mg monotherapy followed by relugolix combination therapy as described earlier, each for 12 weeks) and received double-blind treatment for 24 weeks. Investigational products (ie, relugolix, placebo tablet, estradiol, norethisterone acetate, and placebo capsule) were provided together in blister packs; the placebo for both the relugolix tablet and relugolix combination treatment were manufactured to match in size, shape, and colour. There was a subsequent 30-day safety follow-up period. Visits occurred at baseline and every 4 weeks for 24 weeks. All patients enrolled in the study were provided with a smart phone device (either HTC Desire 320 or Samsung Galaxy J5 [2016] MN Variant) with an application for a patient eDiary, with which they recorded compliance with study treatment, menstrual bleeding, endometriosis-associated pain, and the use of analgesics. Intensity of dysmenorrhoea, non-menstrual pelvic pain, and dyspareunia were reported by patients using the NRS. Protocol-specified analgesic medication for breakthrough pain was standardised (appendix p 12). Patients were required to complete the eDiary by midnight each day and recall was only 24 h, except for analgesics (72 h), which prevented delayed data entry that could have incorporated recall bias and allowed for close monitoring of eDiary completion and compliance. During the study, participants completed the Patient Global Assessment (PGA) for dysmenorrhoea and non-menstrual pelvic pain at screening, baseline, and every 4 weeks at study visits, and the Patient Global Impression of Change (PGIC) during the run-in, at week 12, and at week 24. Patients completed the endometriosis Health Profile-30 (EHP-30) at screening, week 12, and week 24, intentionally coinciding at week 24 with end of treatment. The EHP-30 is a survey designed from the patient's perspective to assess health-related quality of life in endometriosis. The EHP-30 Pain Domain assesses the effect of pain on function and includes 11 questions that ask patients how often during the last 4 weeks they have been unable to or found it difficult to perform or engage in certain activities due to their endometriosis (responses are never, rarely, sometimes, often, and always). Items within the EHP-30 domains were summed to create a raw score, and then each scale score was transformed into a normalised score ranging from 0 (best health status) to 100 (worst health status). The EHP-30, PGA for pain, and PGICs were collected using a tablet device (Acer Switch 10V). The PGA for dysmenorrhoea, NMPP, and function were collected by paper. Bone mineral density data were derived from dual x-ray absorptiometry using algorithms coded into computer software supervised by human operators. The software is provided by various third parties; specifically, DXA scanner software produced by GE Lunar (Madison, WI, USA) and Hologic (Bedford, MA, USA). Z scores were calculated by subtracting the mean bone mineral density for a healthy sex, ethnicity, and age-matched adult population from the participant bone mineral density score and dividing the result by the SD of the bone mineral density values in the population used to determine the mean bone mineral density. All DXA images were submitted, processed, and reviewed by a central radiology laboratory (Clario [previoulsy Bioclinica], San Mateo, CA). Safety evaluations included physical examinations, monitoring vital signs, adverse events, clinical laboratory parameters, 12-lead electrocardiograms, bone mineral density measured by dual-energy x-ray absorptiometry, and endometrial biopsies. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA [version 22]) and severity of adverse events was evaluated by the investigator based on the National Cancer Institute's Common Terminology for Adverse Events (version 5.0).

Outcomes

The co-primary outcomes in both trials were the proportion of responders at the end of treatment (week 24) based on the dysmenorrhoea NRS score in the relugolix combination therapy group compared with the placebo group, and the proportion of responders at the end of treatment based on the non-menstrual pelvic pain NRS score in the relugolix combination therapy group compared with the placebo group.[19,20] The responder thresholds were developed to identify the magnitude of change in NRS that was meaningful to patients. Those with increased use in analgesics were classified as non-responders (appendix p 13). We assessed the proportion of responders in the delayed relugolix combination therapy group compared with placebo as a secondary endpoint.

Key secondary outcomes at week 24 included change in the relugolix combination therapy group compared with the placebo group in the following: EHP-30 pain domain score[21]; average dysmenorrhoea NRS score; average non-menstrual pelvic pain NRS score; average overall pelvic pain NRS score; average dyspareunia NRS scores; proportion of patients not using opioids for endometriosis-associated pain; and proportion of patients not using analgesics for endometriosis-associated pain (SPIRIT 1) or change from baseline in analgesic use (based on average daily pill count; SPIRIT 2). Further details for each

endpoint, along with type 1 error protected secondary endpoints, are described in the appendix (p 21). Additional (non-type-1-error-protected) secondary endpoint analyses examined the mean change and percentage change from baseline in average dysmenorrhea, non-menstrual pelvic pain, and dyspareunia NRS scores as well as EHP-30 over time by visit. Safety endpoints included treatment-emergent adverse events, percentage change from baseline in bone mineral density, and endometrial biopsy histology, as described in the appendix (p 21). The co-primary outcomes, secondary outcomes, and safety analyses were all assessed in the modified intention-to-treat population, which included all randomly assigned participants who received at least one dose of assigned study treatment.

Statistical analysis

In each study, a sample size of 200 patients per treatment group was planned to provide more than 90% power to detect a difference of 20% or more in each co-primary endpoint between the relugolix combination therapy and placebo groups, assuming a placebo responder rate of 30–35% (based on a range of responder rates observed in similar phase 3 endometriosis trials), and a dropout rate of 20%,[8] at a two-sided α level of 0·05.

The comparison for each co-primary endpoint (dysmenorrhoea or non-menstrual pelvic pain) was done using a logistic regression model with responder status as a dependent variable, treatment as the main effect, baseline pain score (dysmenorrhoea or non-menstrual pelvic pain), and the stratification factors (geographical region [North America *vs* all other regions]; years since surgical endometriosis diagnosis [<5 years *vs* ≥5 years]) as covariates.

Before unmasking, an independent psychometrician developed meaningful change thresholds in NRS scores for the coprimary endpoints.[22] The PGA for dysmenorrhoea and non-menstrual pelvic pain served as the primary anchor to correlate with changes in NRS scores to derive the respective meaningful change thresholds; the PGIC served as a secondary anchor. Cumulative distribution functions and probability density function curves were developed to visualise a statistically meaningful change using the entire distribution of patient responses and triangulated with information from patient exit interviews to support what was considered a meaningful change to patients.[22,23] Similar anchor-based analyses were undertaken for the EHP-30 that used PGA for function as the anchor. These data established meaningful change thresholds of –2·8 points for dysmenorrhoea, –2·1 points for non-menstrual pelvic pain, and –20 points for the functional endpoint of the EHP-30 pain domain score.

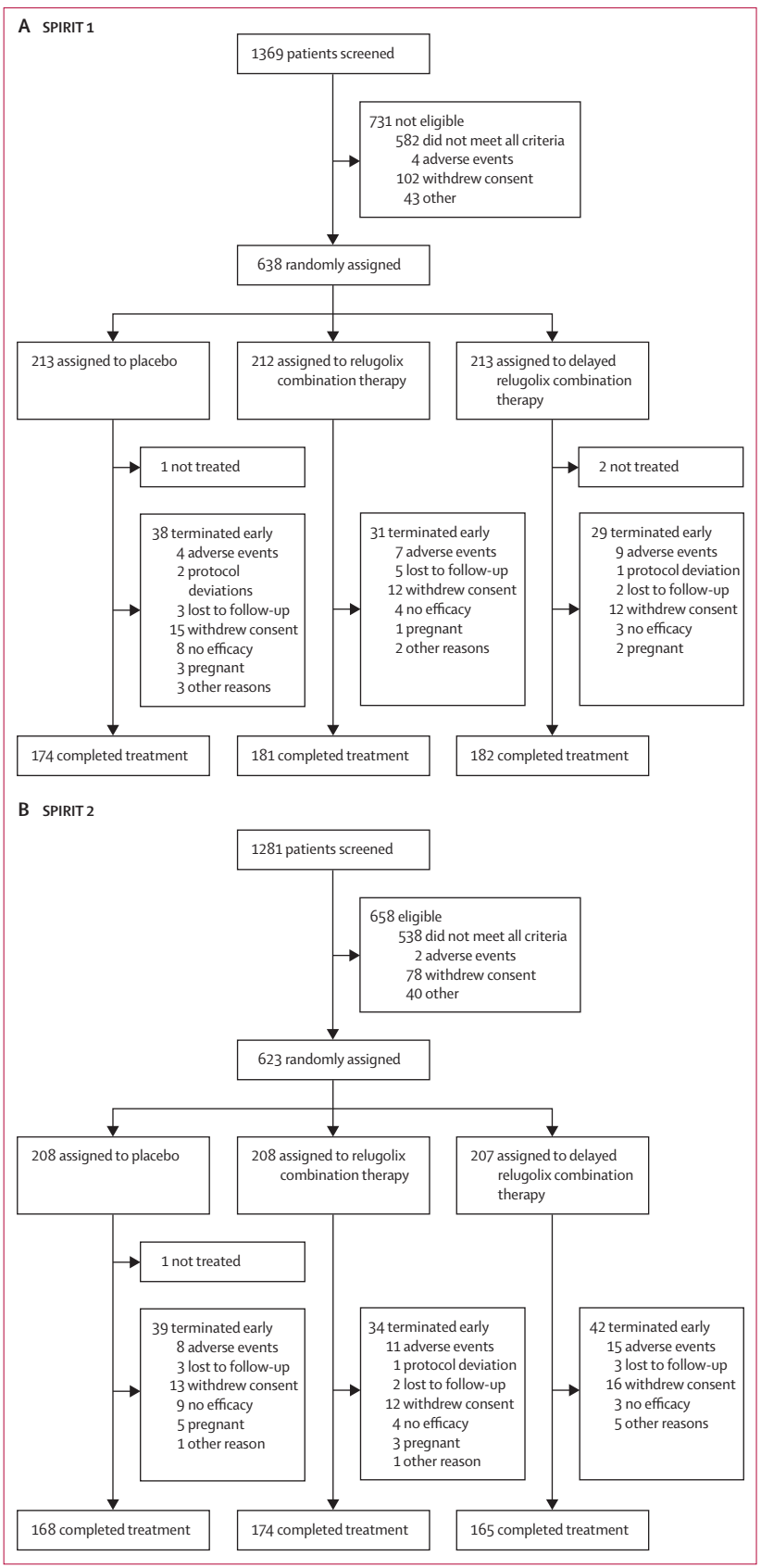

Figure 1. **Trial profiles of SPIRIT 1 (A) and SPIRIT 2 (B)**
Six randomly assigned patients from one study site were excluded from all efficacy and safety analyses due to non-compliance with International Council for Harmonisation E6 R2 Good Clinical Practice guidelines and identified data integrity issues.

	SPIRIT 1			SPIRIT 2		
	Placebo (n=212)	Relugolix combination therapy (n=212)	Delayed relugolix combination therapy (n=211)	Placebo (n=204)	Relugolix combination therapy (n=206)	Delayed relugolix combination therapy (n=206)
Age, years	34·2 (6·6)	33·9 (6·3)	34·3 (6·7)	33·6 (6·5)	33·8 (6·7)	33·7 (6·8)
Body-mass index	26·1 (6·4)	25·6 (6·0)	25·7 (6·1)	25·8 (6·0)	26·1 (6·5)	26·2 (5·9)
Race*						
White	193 (91%)	194 (92%)	194 (92%)	183 (90%)	186 (90%)	188 (91%)
Black	12 (6%)	13 (6%)	10 (5%)	12 (6%)	14 (7%)	10 (5%)
Other	7 (3%)	5 (2%)	7 (3%)	9 (4%)	6 (3%)	8 (4%)
Geographical region						
North America	40 (19%)	40 (19%)	41 (19%)	49 (24%)	50 (24%)	50 (24%)
Europe	143 (67%)	146 (69%)	143 (68%)	122 (60%)	124 (60%)	122 (59%)
All other regions	29 (14%)	26 (12%)	27 (13%)	33 (16%)	32 (16%)	34 (17%)
Time since surgical diagnosis of endometriosis, years	3·8 (3·3)	3·8 (3·2)	4·4 (4·1)	3·8 (3·0)	4·1 (3·5)	4·2 (3·5)
<5 years	148 (70%)	151 (71%)	135 (64%)	143 (70%)	137 (67%)	135 (66%)
5–10 years	64 (30%)	61 (29%)	76 (36%)	61 (30%)	69 (33%)	71 (34%)
Bone mineral density, Z score†						
Lumbar spine	0·18 (1·1)	0·17 (1·1)	0·19 (1·1)	0·35 (1·0)	0·23 (1·1)	0·25 (1·1)
Total hip	0·05 (0·9)	−0·01 (0·9)	0·03 (0·9)	0·12 (1·0)	0·1 (1·0)	0·06 (1·0)
Patient-reported outcome measures						
Dysmenorrhoea NRS score‡	7·1 (1·7)	7·2 (1·7)	7·0 (1·8)	7·0 (1·6)	7·1 (1·6)	6·9 (1·5)
<7	90 (43%)	84 (40%)	97 (46%)	96 (47%)	92 (45%)	97 (47%)
≥7	122 (58%)	128 (60%)	114 (54%)	108 (53%)	114 (55%)	109 (53%)
Non-menstrual pelvic pain NRS score§	5·8 (1·8)	5·9 (2·0)	5·6 (2·0)	5·5 (1·9)	5·8 (1·9)	5·5 (1·9)
<4	43 (20%)	43 (20%)	53 (25%)	45 (22%)	42 (20%)	55 (27%)
≥4	169 (80%)	169 (80%)	158 (75%)	159 (78%)	164 (80%)	151 (73%)
Dyspareunia NRS score‡	5·7 (2·3)	5·7 (2·3)	5·3 (2·4)	5·3 (2·3)	5·5 (2·3)	5·4 (2·1)
<7	113/165 (68%)	112/174 (64%)	126/176 (72%)	131/162 (81%)	127/173 (73%)	129/167 (77%)
≥7	52/165 (32%)	62/174 (36%)	50/176 (28%)	31/162 (19%)	46/173 (27%)	38/167 (23%)
EHP-30 pain domain§	55·5 (16·0)	58·3 (16·7)	55·5 (16·8)	55·0 (16·2)	56·2 (17·1)	55·5 (15·2)
<50	67/208 (32%)	60/208 (29%)	70/208 (34%)	74 (36%)	62/203 (31%)	62 (30%)
≥50	141/208 (67%)	148/208 (71%)	138/208 (66%)	130 (64%)	141/203 (69%)	144 (70%)
Analgesic use at baseline¶						
Only non–opioids	137 (65%)	128 (60%)	124 (59%)	97 (48%)	97 (47%)	94 (46%)
Opioids‖	52 (26%)	64 (30%)	65 (31%)	95 (47%)	100 (49%)	101 (49%)

Data are mean (SD) or n (%). Denominators for dyspareunia differ from the column total due to a subset of patients who were sexually active with NRS >0 and denominators for EHP-30 pain domain scores differ from the column total due to missing EHP-30 baseline data. BMD=bone mineral density. EHP-30=Endometriosis Health Profile 30-item Questionnaire. NRS=numerical rating scale. *Race was reported by the patient. Other includes Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, and multiple. †Z scores are based on analysis of corrected bone mineral density data as assessed by a central radiology laboratory. ‡Scores for dysmenorrhoea, dyspareunia, and non-menstrual pelvic pain could range from 0 (no pain) to 10 (pain as bad as you can imagine) and were recorded in an electronic daily diary. §EHP-30 assesses the effect of pain on normal daily activity including the ability to stand, sit, walk, exercise, sleep, to participate in social events and jobs, and the effect on appetite, ranging from 0 (worst health status) to 100 (best health status) based on transformed scores. ¶Baseline refers to the 35-day run-in period. ||Includes opioids as monotherapy and opioids plus non-opioids as combination therapy.

Table 1: **Demographics and baseline characteristics**

Missing data handling rules were implemented for deriving responder status over the last 35 days of treatment (week 24), considering duration of treatment exposure and compliance with pain score entry on the daily electronic diary.

Analyses of the co-primary and seven key secondary efficacy endpoints for each study were done at an overall α level of 0·05 (two-sided) comparing relugolix combination therapy with placebo. A fixed-sequence testing procedure was used to maintain the family-wise type I error rate by testing the co-primary and key secondary endpoints sequentially. In each study, the two co-primary endpoints were tested first, and if the p value was less than 0·05 for both co-primary endpoints, the seven key secondary efficacy endpoints were tested sequentially per the testing procedure for the study.

Additional details on the design, missing data rules, and analysis methods are provided in the appendix (p 21). The protocol is also provided in the appendix (p 36). We used SAS (version 9.2) for statistical analyses of the trials. An independent Data Monitoring Committee was established consisting of experts in women's health, clinical study safety monitoring, and statistics. This committee evaluated the safety of study participants on an ongoing basis. The studies are registered at ClinicalTrials.gov (SPIRIT 1 [NCT03204318] and SPIRIT 2 [NCT03204331]) and EudraCT (SPIRIT 1 [2017–001588–19] and SPIRIT 2 [2017–001632–19]).

Role of the funding source

The funder of the study designed the studies in collaboration with members of the Steering Committee. The funder had a role in data collection, data analysis, data interpretation, and writing of the report. The Steering Committee worked with the funder to interpret the data. Funder authors collaborated with academic authors in the development of the manuscript.

Results

1369 patients signed the informed consent form for SPIRIT 1, of whom 1105 entered the single-blind run-in period, and of whom 638 were randomly assigned between Dec 7, 2017, and Dec 4, 2019, at 124 centres globally to receive relugolix combination therapy (212 [33%]), placebo (213 [33%]), or relugolix delayed combination therapy (213 [33·3%]; figure 1A). There were 731 patients who were not eligible; the most common reason was not meeting protocol-specified NRS scores at the end of the run-in period for dysmenorrhea or non-menstrual pelvic pain (105 [18%] patients). 98 (15%) patients terminated study participation early; reasons included adverse events, protocol deviations, loss to follow-up, withdrawal of consent, reported no efficacy, pregnancy, or other. In SPIRIT 2, a total of 1281 patients signed the informed consent form, 1069 patients entered the single-blind run-in period, and 623 patients were randomly assigned at 95 centres globally between Nov 1, 2017 and Oct 4, 2019, to receive relugolix combination therapy (208 [33%]), placebo (208 [33%]), or relugolix delayed combination therapy (207 [33·2%]; figure 1B). 658 patients were not eligible; the most common reason was not meeting protocol-specified NRS scores at the end of the run-in period for dysmenorrhea or non-menstrual pelvic pain (118 [22%] patients). Six randomly assigned patients from one study site were excluded from all efficacy and safety analyses due to non-compliance with International Council for Harmonisation E6 R2 Good Clinical Practice guidelines at the study site and identified data integrity issues. 115 (18%) patients terminated study participation early; the reasons were the same as for SPIRIT 1. Three patients in SPIRIT 1 were randomly assigned but did not receive a study drug (two in the delayed relugolix group who were randomly assigned in error and one in the placebo group who was discontinued) and one patient in the placebo group of SPIRIT 2 was randomly assigned in error and so did not receive a study drug. 434 (68%) of 635 patients in SPIRIT 1 and 415 (67%) of 616 patients in SPIRIT 2 had been surgically diagnosed with endometriosis in the past 5 years. 185 (29%) patients in SPIRIT 1 and 288 (47%) in SPIRIT 2 were taking opioids for pain relief at baseline (table 1).

In the relugolix combination therapy group, 158 (75%) of 212 patients in SPIRIT 1 and 155 (75%) of 206 patients in SPIRIT 2 met the dysmenorrhoea responder definition compared with 57 (27%) patients receiving placebo in SPIRIT 1 and 62 (30%) patients in SPIRIT 2 (figure 2). The difference in dysmenorrhoea responder rates between

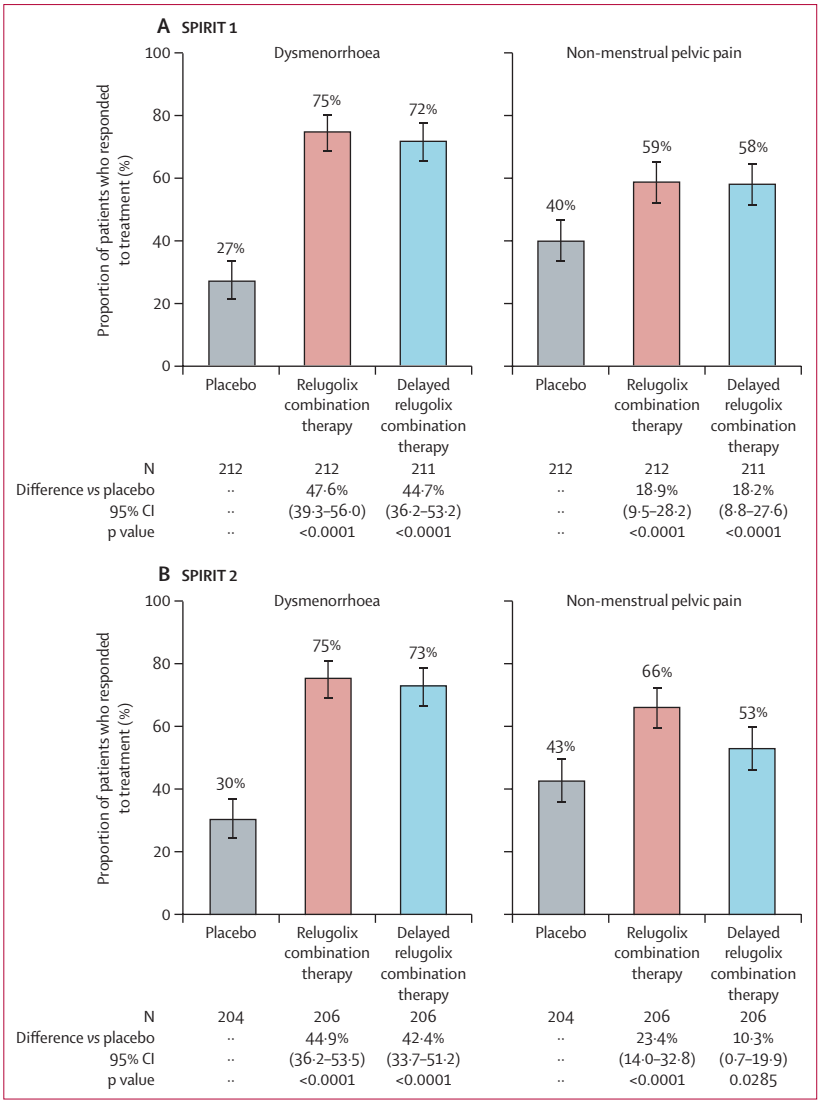

Figure 2: **Dysmenorrhoea and non-menstrual pelvic pain responders in SPIRIT 1 (A) and SPIRIT 2 (B)**
Error bars represent 95% CIs. *Primary endpoint analysis.

	SPIRIT 1					SPIRIT 2				
	Placebo (n=212)	Relugolix combination therapy (n=212)	Delayed relugolix combination therapy (n=211)	Difference between Relugolix combination therapy *vs* placebo (95% CI)	p value	Placebo (n=204)	Relugolix combination therapy (n=206)	Delayed relugolix combination therapy (n=206)	Difference between Relugolix combination therapy *vs* placebo (95% CI)	p value
Dysmenorrhoea responders	57 (27%)	158 (75%)	151 (72%)	47·6% (39·3 to 56·0)	<0·0001	62 (30%)	155 (75%)	150 (73%)	44·9% (36·2 to 53·5)	<0·0001
Non-menstrual pelvic pain responders	84 (40%)	124 (59%)	122 (58%)	18·9% (9·5 to 28·2)	<0·0001	187 (43%)	136 (66%)	109 (53%)	23·4% (14·0 to 32·8)	<0·0001
Change in EHP-30 pain domain*	–18·7 (1·8)	–33·8 (1·8)	–32·1 (1·8)	–15·1 (–19·7 to –10·5)	<0·0001	–19·9 (1·7)	–32·2 (1·7)	–30·8 (1·7)	–12·3 (–16·7 to –7·9)	<0·0001
Change in dysmenorrhoea NRS	–1·8 (0·2)	–5·1 (0·2)	–4·9 (0·2)	–3·3 (–3·8 to –2·8)	<0·0001	–2·0 (0·2)	–5·1 (0·2)	–4·6 (0·2)	–3·2 (–3·7, to –2·7)	<0·0001
Change in non-menstrual pelvic pain NRS	–2·0 (0·2)	–2·9 (0·2)	–2·8 (0·2)	–0·9 (–1·4 to –0·4)	0·0002	–2·0 (0·2)	–2·7 (0·2)	–2·5 (0·2)	–0·7 (–1·2 to –0·3)	0·0012
Change in overall pelvic pain NRS	–1·9 (0·17)	–3·1 (0·2)	–2·9 (0·2)	–1·1 (–1·6 to –0·7)	<0·0001	–2·0 (0·2)	–2·9 (0·2)	–2·7 (0·2)	–0·9 (–1·4 to –0·5)	<0·0001
Patients not using opioids during treatment	162 (76%)	182 (86%)	174 (83%)	9·4% (2·0 to 16·8)	0·0005	135 (66%)	169 (82%)	168 (82%)	15·9% (7·5% to 24·2)	<0·0001
Change in dyspareunia NRS	–1·7 (0·2)	–2·4 (0·2)	–2·2 (0·2)	–0·7 (–1·3 to –0·1)	0·0149	–1·9 (0·2)	–2·4 (0·2)	–2·3 (0·2)	–0·5 (–1·0 to 0·0)	0·0371
Patients not using analgesics for endometriosis-associated pain during treatment†	65 (31%)	119 (56%)	123 (58%)	25·5% (16·4% to 34·6%)	<0·0001	48 (24%)	112 (54%)	118 (57%)	30·8% (21·9% to 39·8%)	<0·0001
Change in daily analgesic use‡	–0·4 (0·1)	–0·5 (0·1)	–0·6 (0·1)	–0·1 (–0·3 to 0·1)	0·4094	–0·4 (0·1)	–0·5 (0·1)	–0·5 (0·1)	–0·1 (–0·3 to 0·0)	0·1141

Data are n (%) or least squares means (SE) unless otherwise stated. Changes are from baseline to week 24 (end of treatment). EHP-30=Endometriosis Health Profile 30-item Questionnaire. mITT=modified intention-to-treat. NRS=numerical rating scale. *EHP-30 assesses the effect of pain on normal daily activity including the ability to stand, sit, walk, exercise, sleep, to participate in social events and jobs, and the effect on appetite. †SPIRIT2 data for patients not using analgesics for endometriosis-associated pain were from a post-hoc exploratory analysis. ‡SPIRIT 1 data for change in daily analgesic use were from a post-hoc exploratory analysis.

***Table 2*: Co-primary and key secondary efficacy endpoints**

relugolix combination therapy and placebo was 47·6% (95% CI 39·3–56·0) in SPIRIT 1 and 44·9% (36·2–53·5) in SPIRIT 2, both p<0·0001. For non-menstrual pelvic pain, 124 (59%) patients in SPIRIT 1 and 136 (66%) patients in SPIRIT 2 met the responder definition in the relugolix combination therapy group compared with 84 (40%) patients receiving placebo in SPIRIT 1 and 87 (43%) in SPIRIT 2. The difference in non-menstrual pelvic pain responders between placebo and relugolix combination therapy was 18·9% (95% CI 9·5–28·2) in SPIRIT 1 and 23·4% (14·0–32·8) in SPIRIT 2, both p<0·0001. The response rates in the delayed relugolix combination therapy group were similar in both studies; for dysmenorrhoea, 151 (72%) of 211 patients in SPIRIT 1 and 150 (73%) of 206 patients in SPIRIT 2 had a response, and for non-menstrual pelvic pain 122 (58%) patients in SPIRIT 1 and 109 (53%) patients in SPIRIT 2 had a response (figures 2A, 2B). The results of five sensitivity analyses for both co-primary endpoints were consistent with the primary analysis for each endpoint (appendix p 14).

Relugolix combination therapy compared with placebo achieved all ranked key secondary endpoints in SPIRIT 1 and in six of seven in SPIRIT 2 (table 2). In the relugolix combination groups, between baseline and week 24, the least squares mean NRS for dysmenorrhoea decreased from 7·3 to 1·8 in SPIRIT 1 and from 7·2 to 1·7 in SPIRIT 2 (both p<0·0001 *vs* placebo), representing a 73% reduction from baseline in SPIRIT 1 and a 75% reduction from baseline in SPIRIT 2. The least squares mean NRS for dysmenorrhoea in the placebo groups was 5·0 in SPIRIT 1 and 4·9 in SPIRIT 2 at 24 weeks (appendix p 10). The mean non-menstrual pelvic pain NRS score also decreased significantly from baseline to week 24 in women treated with relugolix combination therapy compared with placebo: from 5·8 to 2·9 (50% reduction; p=0·0002) in SPIRIT 1 and from 5·9 to 2·9 (49% reduction; p=0·0012) in SPIRIT 2 (appendix p 11). Assessment of time to response suggested benefit as early as 8 weeks after starting treatment for dysmenorrhoea and 12 weeks for non-menstrual pelvic pain (appendix pp 10–11). Women treated with relugolix combination therapy reported significant improvement in overall pelvic pain and dyspareunia compared with those who received placebo (table 3). The effects of pain on daily function, assessed by the EHP-30 pain domain, improved significantly in the relugolix combination therapy group compared with placebo. More women in the relugolix combination groups were opioid free at week 24 than in the placebo group. The proportion of

	SPIRIT 1			SPIRIT 2		
	Placebo (n=212)	Relugolix combination therapy (n=212)	Delayed relugolix combination therapy (n=211)	Placebo (n=204)	Relugolix combination therapy (n=206)	Delayed relugolix combination therapy (n=206)
Adverse events	140 (66%)	151 (71%)	163 (77%)	153 (75%)	166 (81%)	168 (82%)
Suicidal ideation	1 (<1%)	0	1 (<1%)	1 (<1%)	2 (1%)	2 (1%)
Death	0	0	0	0	0	0
Adverse events of grade 3 or higher	12 (6%)	10 (5%)	9 (4%)	7 (3%)	14 (7%)	12 (6%)
Serious adverse events	5 (2%)	3 (1%)	3 (1%)	4 (2%)	9 (4%)	6 (3%)
Adverse events leading to trial-drug discontinuation	4 (2%)	8 (4%)	9 (4%)	8 (4%)	11 (5%)	15 (7%)
Adverse events reported in more than 5% of patients in any group						
Headache	46 (22%)	57 (27%)	67 (32%)	64 (31%)	81 (39%)	79 (38%)
Nasopharyngitis	12 (6%)	13 (6%)	10 (5%)	17 (8%)	29 (14%)	14 (7%)
Hot flush	21 (10%)	22 (10%)	71 (34%)	7 (3%)	28 (14%)	72 (35%)
Toothache	3 (1%)	5 (2%)	3 (1%)	7 (3%)	18 (9%)	7 (3%)
Back pain	5 (2%)	8 (4%)	7 (3%)	7 (3%)	12 (6%)	12 (6%)
Nausea	11 (5%)	13 (6%)	9 (4%)	6 (3%)	12 (6%)	9 (4%)
Arthralgia	2 (1%)	4 (2%)	9 (4%)	7 (3%)	11 (5%)	10 (5%)
Bone density decreased	4 (2%)	5 (2%)	8 (4%)	5 (2%)	11 (5%)	13 (6%)
Libido decreased	1 (<1%)	5 (2%)	7 (3%)	4 (2%)	11 (5%)	8 (4%)
Urinary tract infection	6 (3%)	4 (2%)	9 (4%)	5 (2%)	11 (5%)	10 (5%)
Acne	13 (6%)	2 (1%)	1 (<1%)	11 (5%)	7 (3%)	7 (3%)
Vitamin D decreased	15 (7%)	4 (2%)	8 (4%)	3 (1%)	1 (1%)	0

Data are n (%). The remaining adverse events each occurred in less than ten patients in any group.

Table 3: **Adverse events**

women not requiring either opioid or non-opioid analgesics at week 24 was also significantly higher in the relugolix combination therapy group than the placebo group in both SPIRIT 1 (prespecified key secondary endpoint) and in SPIRIT 2 (post hoc analysis; table 2).

The overall incidence of adverse events, both serious and non-serious, was similar among treatment groups (table 3). The most common adverse events were headache and nasopharyngitis (table 3). Hot flushes were reported more frequently in the delayed relugolix combination therapy group than in the relugolix combination therapy or placebo groups, and mostly occurred during the first 12 weeks of treatment (data not shown). There were nine reports of suicidal ideation across both studies including the run-in period, all in women with a self-reported psychiatric history (placebo run-in [2], placebo [2], relugolix combination therapy [2], and delayed relugolix combination therapy [3]); all patients who had suicidal ideation discontinued study participation.

Least squares mean percentage changes from baseline to week 12 and 24 in bone mineral density at the lumbar spine and total hip were less than 1% in patients treated with relugolix combination therapy in both studies (figure 3; appendix pp 15–16). In the delayed relugolix combination therapy groups, bone mineral density at the lumbar spine and total hip substantially declined at week 12 with relugolix monotherapy, which stabilised with transition to relugolix combination therapy.

No clinically important differences were evident in vital signs including blood pressure or laboratory parameters including liver function tests and lipids (appendix pp 17–18). Most women treated with relugolix combination therapy or delayed relugolix combination therapy reported no bleeding or infrequent bleeding compared with the placebo group, in which most women reported normal bleeding or irregular or infrequent bleeding (appendix p 19). Eligible patients who completed SPIRIT 1 or 2 could enrol in an 80-week open-label extension study to collect additional efficacy and safety data. In patients who did not continue into the long-term study extension, menses resumed after cessation of relugolix combination therapy or delayed relugolix combination therapy, other than in those patients with a known reason for non-recovery (eg, pregnancy, medications, or surgery). The median time of menses return was 31 days for both the relugolix combination group (IQR 21–36) and delayed relugolix combination group (24–36). 90 (94%) of the 96 patients with menstruation status follow-up from the relugolix combination group and 120 (91%) of the 132 patients with menstruation status follow up from the delayed group resumed menses within 2 months of stopping treatment. There were 14 pregnancies during the study

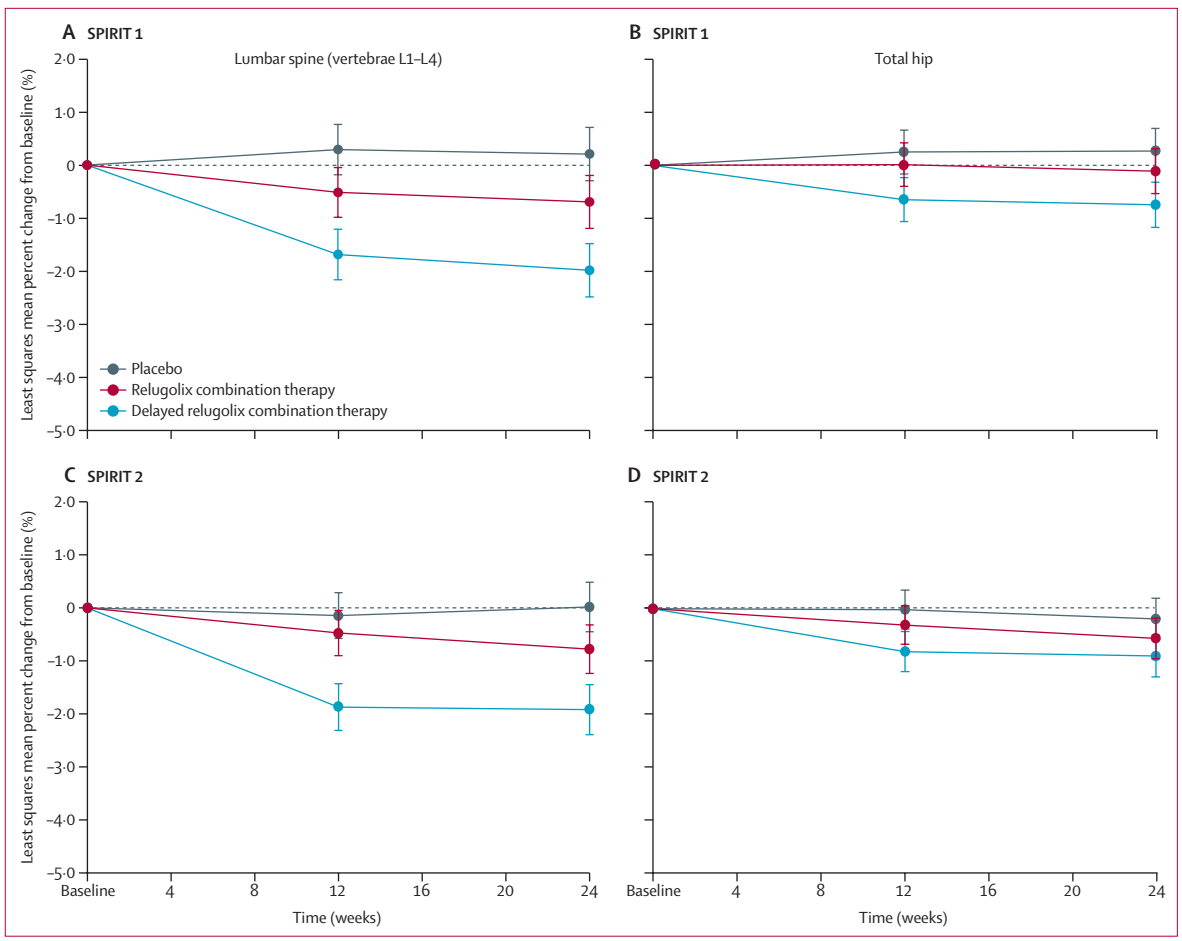

Figure 3: **Percent change from baseline to 24 weeks in bone mineral density for lumbar spine in SPIRIT 1 (A) and SPIRIT 2 (C) and total hip in SPIRIT 1 (B) and SPIRIT 2 (D)**
Error bars indicate 95% CIs.

period (placebo [eight], relugolix combination therapy [four], and delayed relugolix combination therapy [two]). Of the six pregnancies in the relugolix groups, three occurred during the first month of treatment, and two patients who were pregnant had poor compliance by eDiary entry. No congenital anomalies were reported in pregnancies in which the outcome is known (appendix p 20). No cases of endometrial hyperplasia or endometrial cancer were reported.

Discussion

In these two randomised, placebo-controlled, phase 3 trials in women with endometriosis-associated pain, a significantly higher proportion of women treated with relugolix combination therapy responded to treatment compared with those treated with placebo—showing improvement in dysmenorrhoea and non-menstrual pelvic pain greater than or equal to predetermined meaningful change thresholds with no increase in analgesic use. Most patients had moderate or severe dysmenorrhoea and non-menstrual pelvic pain at study entry. Baseline EHP-30 pain domain scores were 50 or higher, reflecting substantial negative effect of pain on daily activities. Over 90% of patients in both trials used analgesics at baseline to manage pain, including opioids in 185 (29%) women in SPIRIT 1 and 288 (47%) women in SPIRIT 2. The findings of high baseline pain intensity, substantial physical limitations, and high analgesic use are evidence of a pronounced effect of disease on these women.

Although the studies were designed with a placebo comparator, we considered an active control with an accepted treatment for endometriosis. However, because the studies were multinational, a potential active comparator would have to have been approved for treatment of endometriosis in all countries participating in the study. Combined hormonal contraceptives, although commonly used, are not approved for treatment of endometriosis, and their off-label use for this indication is not supported by good quality, adequate, and well controlled trials.[24] With the known bone mineral density loss that occurs with some treatments for endometriosis (eg, leuprolide),[25] such controls were not favoured for the

24 week pivotal studies, given that the goal of the programme was to develop a product for long-term treatment and leuprolide use in this setting is limited to 6 months or 1 year with hormonal (oestrogen and progestin) add-back therapy.[26–28] Use of placebo allowed for a clearer characterisation of the safety and efficacy profile of relugolix, a new chemical entity, that would not be possible with an active comparator.

We selected the doses of estradiol and norethisterone acetate for combination with relugolix on the basis of dose-finding studies for commercially available estradiol and norethisterone acetate combination products.[29] Results from these studies showed that treatment with a 1 mg dose of estradiol alone in patients with available biopsies was associated with endometrial disordered proliferative phase in 21 (9%) of 247 patients and with endometrial hyperplasia in 36 (15%) of 247 patients.[30] The combination of 1 mg estradiol and 0·5 mg norethisterone acetate prevented such findings and was associated with the lowest rate of unscheduled bleeding.[31] In addition, the adequacy of the combination of estradiol 1 mg and norethisterone acetate 0·5 mg with relugolix was supported by a 6-week study that showed prevention of vasomotor symptoms and increase in markers of bone turnover compared with relugolix monotherapy, and systemic oestradiol concentrations in a therapeutically effective range.[32]

Improvements in dysmenorrhoea and non-menstrual pelvic pain with relugolix combination therapy were observed as early as 4 weeks, with maximum effect at 8 weeks for dysmenorrhoea and at 12 weeks for non-menstrual pelvic pain, and maintained at 24 weeks. The higher percentage of women with reduction in dysmenorrhoea (73–74%) compared with non-menstrual pelvic pain (49–50%) probably reflects the mechanism of action of relugolix, which inhibits gonadal steroids—the driver of menstruation. In the time period of 90 days to the end of treatment, nearly three-quarters of patients who received relugolix combination therapy or delayed relugolix combination therapy had no bleeding or infrequent bleeding, which is internally consistent with the responder rate for dysmenorrhoea. In contrast, the mechanisms that underlie non-menstrual pelvic pain are not as well understood and are probably multifactorial, including fibrosis, adhesions, chronic inflammation, and central sensitisation that might be less responsive to suppression of oestradiol than dysmenorrhoea. Analgesics and longer duration of quiescent endometriosis through GnRH receptor antagonism together might address this complex pain presentation.

Benefits with relugolix combination therapy were also observed for key secondary endpoints. Improvements in the EHP-30 pain domain score indicated that patient function improved as a consequence of decreased pain. Additionally, there were reductions in dyspareunia, a common physically and psychologically distressing symptom associated with endometriosis,[33] and reduced analgesic and opioid use.

The incidence of serious and non-serious adverse events was generally similar between the relugolix combination treatment and placebo groups. The mechanism for nasopharyngitis is not known, although it is a commonly reported adverse event in clinical trials across therapeutic areas, including for another GnRH receptor antagonist, elagolix, for uterine fibroids.[34] Although participants were required to use non-hormonal contraception during study participation, six pregnancies were reported in the active treatment groups. Half occurred in the first month of treatment. Higher rates of depression and suicide have been described in women with endometriosis than in those in the general population.[6,35] In the SPIRIT 1 and 2 studies, suicidal ideation was reported with similar frequency in all treatment groups and occurred in patients with previous psychiatric history. The observed change from baseline in bone mineral density (<1%) is not considered clinically meaningful. Loss in bone density was significantly greater and hot flushes more common in women treated with delayed relugolix combination than those treated with relugolix combination therapy, suggesting that the dose of estradiol in relugolix combination therapy might be adequate to maintain oestradiol concentrations in a therapeutically effective range.

Current hormonal treatments focus on suppression of endogenous oestrogen production with associated inhibition of endometriosis tissue proliferation and inflammation, requiring a trade-off between benefit and risk of a therapeutically induced hypoestrogenic state.[1,2] GnRH receptor antagonism is an effective and approved strategy to manage endometriosis-associated pain.[36,37] In replicate studies of high-dose monotherapy (200 mg twice a day) of another GnRH receptor antagonist, elagolix, responder rates at 6 months for dysmenorrhoea were 75% in Elaris EM-I and 77% in Elaris EM-II and for non-menstrual pelvic pain were 62% in both trials. The lower dose of 150 mg daily was less efficacious, with responder rates of 42% in trial 1 and 46% in trial 2 for dysmenorrhoea and 46% for trial 1 and 52% for trial 2 for non-menstrual pelvic pain, compared with placebo rates of 23% in Elaris EM-I and 25% in Elaris EM-II for dysmenorrhorea and 35% in Elaris EM-I and 41% in Elaris EM-II for non-menstrual pelvic pain.[36] The lower dose also did not reduce dyspareunia.[8] Although the higher dose elagolix regimen showed greater benefit than placebo, it was associated with hypoestrogenic effects of hot flushes and bone mineral density loss, which limit the approved treatment duration to 6 months. Leuprolide acetate (including 1-month and 3-month formulations, also referenced as leuprorelin for studies in Japan), a GnRH agonist, is approved as monotherapy for management of endometriosis, including pain relief and reduction of endometriotic lesions, and in combination with norethisterone acetate for initial management of the painful symptoms of endometriosis and for management of recurrence of symptoms.[25] The total duration of therapy with leuprolide and add-back

therapy should not exceed 12 months because of concerns about bone mineral density loss.[26–28]

The combination of relugolix, estradiol, and norethisterone acetate might provide the therapeutic benefits of GnRH receptor antagonism to suppress endogenous oestradiol concentrations and improve symptoms of endometriosis while minimising the risk of hypoestrogenic-related bone loss and vasomotor symptoms, potentially enabling long-term use. These data, along with studies evaluating the same dose of relugolix combination therapy in women with uterine fibroids,[38] help support the oestrogen threshold hypothesis, which posits that a therapeutically effective oestradiol range would address signs and symptoms of endometriosis or fibroids while minimising hypoestrogenic adverse effects.[39,40] Relugolix combination therapy, as a single daily oral dosing regimen, might offer a simplified approach to the management of these two oestrogen-driven diseases over the longer term.

The SPIRIT studies had limitations. Although the trial population included women with moderate-to-severe endometriosis-associated pain, many screened women did not meet the minimum pelvic pain threshold to participate. Most patients enrolled were White, potentially reflecting under-recognition or under-diagnosis of endometriosis, or suboptimal clinical trial engagement among other races and ethnicities. Treatment duration was 6 months, and these studies cannot address efficacy and safety beyond this period. Use of a placebo-controlled study design did not allow for comparison with mainstays of treatment, including hormonal therapies or surgery. Although it is not possible to determine whether the treatment is superior to these modalities, it can be inferred that relugolix combination therapy is more effective than no treatment or placebo, was associated with the reduction of analgesic use (including opioids), and effectively improved function and other measures of quality of life. Longer term efficacy and safety outcomes will be the subject of future reports based on results of the 80-week open label extension study in eligible patients who completed the SPIRIT studies; database lock for the on-treatment duration has occurred, and post-treatment follow-up for safety, specifically for bone mineral density and menses recovery, is ongoing at the time of publication. Finally, the effects of relugolix combination therapy on ovarian function are an important topic for women of reproductive age. There was evidence of timely return of menses after treatment cessation in women who completed SPIRIT 1 and 2 but did not enter the extension study, and the effect of relugolix combination therapy on ovarian activity will be the subject of a separate manuscript.

Contributors

LCG, SA-S, CMB, MSA, BAL, and NPJ were members of the SPIRIT Steering Committee, which worked with the funder in the development and oversight of the two clinical trials. EB, KD, KW, and NPJ were investigators. For the manuscript, the funder held an organisational meeting with LCG to discuss the data and outline for the manuscript. The Steering Committee and funder reviewed data together for both trials. All authors had access to the data and LCG verified processed data. RBW wrote the first draft of the manuscript, which was distributed to the co-authors for review and editing. The manuscript was substantially revised by the authors, with all authors critically revising the various draft manuscripts with important intellectual content. RBW and YL worked with a medical writer to collate the edits, address comments, and circulate subsequent drafts to co-authors for review, editing, and finalisation. All co-authors provided substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work. All co-authors also approved the final version of the manuscript, agreed to submission of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

LCG reports personal fees from Myovant Sciences. SA-S reports personal fees from Myovant Sciences, Bayer, Abbvie, and UpToDate. CMB reports fees from Myovant Sciences and ObsEva, grants from Bayer Healthcare, and role of Chair of ESHRE Endometriosis Guideline Group. BAL reports personal fees from Myovant Sciences. NPJ reports personal fees from Myovant Sciences during the conduct of the study and personal fees from Guerbet, Abbott, and Roche Diagnostrics. JCAF, YL, and RBW are employees and shareholders of Myovant Sciences. QAW is a former employee of Myovant Sciences. VM is a consultant to Myovant Sciences. All other authors declare no competing interests. The authors did not receive compensation for manuscript writing, review, and revision.

Data sharing

No data sharing agreement has been developed at the time of submission of this manuscript.

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