**53. 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)**

Linda C Giudice, Sawsan As-Sanie, Juan C Arjona Ferreira, Christian M Becker, Mauricio S Abrao,Bruce A Lessey,Eric Brown,Krzysztof Dynowski,Krzysztof Wilk,Yulan Li,Vandana Mathur, Qurratul Ann Warsi, Rachel B Wagman, Neil P Johnson
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**Abstract**

**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.

**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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