Efficacy and safety of relugolix combination therapy in women with uterine fibroids and adenomyosis: subgroup analysis of LIBERTY 1 and LIBERTY 2

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Objective: To assess the effects of relugolix combination therapy in women with uterine fibroids (UFs) and concomitant ultrasound-diagnosed adenomyosis.

Design: This post hoc analysis used pooled data from completers of the pivotal LIBERTY studies. The subgroup of women with adenomyosis and UFs was compared with the overall study population on selected efficacy and safety endpoints.

Subjects: Premenopausal women (aged 18–50 years) with diagnosed UFs (confirmed by ultrasonography) and heavy menstrual bleeding (assessed by the alkaline hematin method).

Intervention: Once-daily relugolix combination therapy (40 mg relugolix, 1 mg estradiol, and 0.5 mg of norethindrone acetate) or placebo for 24 weeks, or delayed relugolix combination therapy (40 mg of relugolix monotherapy for 12 weeks, followed by relugolix combination therapy for 12 weeks).

Main Outcome Measures: Endpoints included the percentage of women with concomitant adenomyosis, the proportion of treatment responders (achieved or maintained a menstrual blood loss <80 mL and $\geq 50\%$ reduction in menstrual blood loss volume from baseline

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URL of the registration site: LIBERTY 1, https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-003727-27 (EudraCT) and https://clinicaltrials.gov/study/NCT03049735 (ClinicalTrials.gov); LIBERTY 2, https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-005113-50 (EudraCT) and https://clinicaltrials.gov/study/NCT03103087 (ClinicalTrials.gov)
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over the last 35 days of treatment), the proportion of women achieving or maintaining amenorrhea over the last 35 days of treatment, and the change from baseline to week 24 in uterine volume and adverse events.

Results: A total of 111 women (18.2%) had a baseline diagnosis of concomitant adenomyosis (37 in the relugolix combination therapy group, 45 in the delayed relugolix combination therapy group, 29 in the placebo group) and were included in this analysis. Of women with adenomyosis, 83.8% in the relugolix combination therapy group were treatment responders compared with 27.6% in the placebo group. Amenorrhea was achieved in 64.9% of women with adenomyosis treated with relugolix combination therapy and in 6.9% of women treated with placebo. The least square mean uterine volume of women with adenomyosis decreased by 22.2% and 5.8% in the relugolix combination therapy and placebo groups, respectively. Results for the above outcomes in the relugolix combination therapy population were similar to the delayed relugolix combination therapy group.

Conclusion: Efficacy outcomes in women with adenomyosis and UFs were comparable with those in women from the overall LIBERTY study population. (Fertil Steril® 2025;■:■–■. ©2025 by American Society for Reproductive Medicine.)

Key Words: Uterine fibroids, adenomyosis, heavy menstrual bleeding, relugolix combination therapy, oral gonadotropin-releasing hormone antagonists

Adenomyosis is a condition characterized by the presence of endometrial glands and stroma within the myometrium. Areas of ectopic endometrium are often surrounded by reactive hypertrophic myometrial tissue, frequently leading to uterine enlargement (1). Adenomyosis has traditionally been diagnosed histopathologically after hysterectomy, an approach that resulted in the perception that the disorder was confined mainly to those in their later reproductive years (2, 3). Previously, typical risk factors for adenomyosis associated with a histopathological diagnosis included prolonged estrogen exposure (late reproductive years), early menarche, short menstrual cycles, elevated body mass index, previous use of oral contraceptives or tamoxifen, parity, and prior uterine surgery (1). However, with improvements in ultrasound and the advent of magnetic resonance imaging (MRI), it is now possible to more reliably identify adenomyosis through imaging, with features that include a globular and often asymmetrically enlarged uterine corpus, abnormalities in the endometrial–myometrial junction and myometrial findings that include cysts and other features such as fan-shaped shading and heterogeneity on ultrasound (4). Improvements in imaging also offer the opportunity to diagnose affected women earlier (2); more recently, it has become apparent that imaging features of adenomyosis can frequently be found in up to 35% of reproductive-age girls and women aged 30 years and below with no history of pregnancy or uterine surgery (5, 6), a circumstance that has led to a reassessment of the pathogenesis of this disorder. The estimated prevalence of adenomyosis varies widely because of unstandardized radiologic diagnostic criteria and definitions and historical challenges with diagnosis (2), ranging from 10% in women with subfertility (7) up to 89% in women with endometriosis (8). As the accuracy of imaging findings is continually refined and standardized, this may allow better estimates of the true prevalence of the disease (2).

Symptoms of adenomyosis include abnormal uterine bleeding—particularly heavy menstrual bleeding (HMB)—dysmenorrhea, dyspareunia, infertility, and a variety of disorders associated with pregnancy, including miscarriage, preterm delivery, pre-eclampsia, fetal malpresentation, and postpartum hemorrhage (9). It has previously been reported that at least 30% of women with adenomyosis are asymptomatic (1); however, the presence of symptoms such as dysmenorrhea, dyspareunia, and pelvic pain is not frequently recorded by clinicians or may be attributed to other uterine pathologies, affecting assessment of adenomyosis symptomatology (3).

Updated adenomyosis guidelines from the Society of Obstetricians and Gynecologists of Canada stated that "Transvaginal sonography should be the first-line modality for imaging of suspected adenomyosis with HMB, pelvic pain, infertility, miscarriage, and adverse pregnancy outcomes [strong, high]," (10) and terminology for the noninvasive diagnosis of adenomyosis has been formalized by the Morphological Uterus Sonographic Assessment (MUSA) group to describe and report ultrasound features of adenomyosis in the myometrium (11). In women with adenomyosis, there is a positive correlation between the number of ultrasound features identified and both the volume of menstrual blood loss (MBL) (12) and the severity of menstrual pain (13, 14). Furthermore, adenomyosis may exist concomitantly with uterine fibroids (UFs) (14), and non-cyclic pelvic pain has been observed more frequently in these patients compared with women who have UF alone (15). In women whose symptoms seem disproportionate to fibroid burden, concomitant adenomyosis should be considered in the differential diagnosis (15).

Currently, the treatment of women with symptomatic adenomyosis is challenging, with much of the literature focused on addressing symptoms of pain and abnormal bleeding associated with adenomyosis (16). Uterine-sparing surgical and image-guided procedures have limited supportive long-term evidence, particularly for fertility (17, 18). There exist several hormonal and non-hormonal therapies that have been prescribed for symptomatic relief, including nonsteroidal anti-inflammatory drugs, combined estrogen–progestin-containing contraceptives, and systemic and intrauterine progestins, including 52 mg levonorgestrel-releasing intrauterine devices and gonadotropin-releasing hormone (GnRH) agonists and antagonists (15, 19–22).

Relugolix is an orally active, nonpeptide GnRH receptor antagonist that suppresses the secretion of gonadotropins, reducing follicular growth and inhibiting ovulation, causing a rapid and reversible decrease in ovarian production of estrogen and progesterone. A retrospective cohort study found that relugolix treatment significantly reduced uterine volume in

patients with concomitant adenomyosis and UF compared with UF alone (23). Relugolix combination therapy, consisting of 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate, is a once-daily single-tablet therapy approved in the United States for the management of HMB associated with UF in premenopausal women, and for the management of moderate-to-severe pain associated with endometriosis. In the EU and several other jurisdictions and administrative districts, relugolix combination therapy is approved for the management of moderate-to-severe symptoms of UF in adult women of reproductive age and symptomatic treatment of endometriosis in women with a history of previous medical or surgical treatment for their endometriosis.

In the LIBERTY 1/2 studies, the safety and efficacy of once-daily relugolix combination therapy were investigated in premenopausal women with UF over 24 weeks. The results of the pivotal studies indicated significant improvement in UF-associated symptoms (including MBL, UF-associated pain, distress from bleeding and pelvic discomfort (BPD), anemia, and uterine enlargement) when compared with placebo (24). Relugolix combination therapy also demonstrated a favorable safety profile with maintenance of bone mineral density in women with UF (24). In addition to improvements in UF-associated symptoms and conditions, women with symptomatic UF treated with relugolix combination therapy experienced substantial improvements in health-related quality of life during LIBERTY 1/2 (25).

When the LIBERTY trials were designed, there was little recognition of adenomyosis as an independent diagnosis, and its presence was not an exclusionary criterion for trial participation. With increased interest in adenomyosis using diagnostic radiologic criteria (11) and country-level diagnostic and management guidelines (10), a post hoc analysis was undertaken to evaluate the prevalence of concomitant adenomyosis at study entry in women who enrolled in the phase 3 LIBERTY studies. In addition, this analysis assessed the effects of relugolix combination therapy for up to 24 weeks in this subpopulation, compared with the overall population.

MATERIALS AND METHODS

Study design

The phase 3, pivotal LIBERTY 1 (ClinicalTrials.gov: NCT03049735) and LIBERTY 2 (NCT03103087) studies enrolled premenopausal women (18–50 years of age) with diagnosed UF (confirmed by ultrasonography) and HMB. Heavy menstrual bleeding was defined as MBL volume of 80 mL or more per cycle for two cycles, or $\geq$160 mL within one cycle and was assessed by the alkaline hematin method. Women were excluded if they had a Z-score of less than −2.0 for bone mineral density at the lumbar spine, total hip, or femoral neck, had other causes of HMB, or were using hormonal therapy. Full details of the design and inclusion and exclusion criteria for the LIBERTY 1/2 studies have been published previously (24). Women were randomized 1:1:1 to receive once-daily relugolix combination therapy or placebo for 24 weeks or delayed relugolix combination therapy (40 mg of relugolix monotherapy for 12 weeks, followed by relugolix combination therapy for 12 weeks). The LIBERTY studies were conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation Harmonised Tripartite Guideline.

To characterize the adenomyosis subgroup of the phase 3 LIBERTY studies, a formal LIBERTY Subgroup Adenomyosis Research Plan was developed, including a brief protocol outline and statistical analysis plan to describe how the subgroup of patients was identified and what analyses would be conducted. In accordance with the standard operating procedures of the central radiology laboratory, the databases for LIBERTY 1/2 that contained only the ultrasound imaging data were unlocked to add the adenomyosis analysis cycle and perform the analysis. Previously locked ultrasound reports were not altered during the adenomyosis analysis. A Note to File that described the process was generated. Baseline ultrasound images from the pooled LIBERTY studies were formally evaluated for adenomyosis post hoc by two expert radiologists using a prespecified classification derived from the MUSA criteria for classification of adenomyosis available at that time (11). Diagnosis of adenomyosis was derived algorithmically and required the presence of at least one of the following three adenomyosis features (described as major): myometrial cysts, hyperechogenic islands or hyperechoic linear striations ("Venetian blinds" or fan-shaped shadowing), or the presence of an asymmetrical thickening and/or globular uterus associated with any other feature; or at least three of the following features (described as minor): heterogeneous uterus, echogenic subendometrial lines and buds, translesional vascularity (using color Doppler), or irregular and/or interrupted junctional zone(s) (Supplemental Fig. 1, available online). An additional assessment of the echostructure of the uterus—uterus heterogeneity that is not explained by the concomitant presence of leiomyoma(s)—was added as a minor feature. Discordance in the derived diagnosis of adenomyosis between the two radiologists was adjudicated in consensus using the same process.

The primary endpoint was the percentage of enrolled women diagnosed with adenomyosis at baseline, as determined by transvaginal ultrasound. Secondary endpoints were consistent with those of the LIBERTY trials (24) and included the proportion of women who were treatment responders (i.e., achieved or maintained an MBL <80 mL and a $\geq$50% reduction in MBL volume from pivotal study baseline over the last 35 days of treatment, as measured by the alkaline hematin method, percentage change in MBL volume from baseline to week 24), proportion of women who achieved or maintained amenorrhea over the last 35 days of treatment (when amenorrhea was defined as: no feminine product returned owing to reported amenorrhea for two consecutive visits, no feminine product returned because of other reasons coupled with other data indicating infrequent non-cyclic bleeding/spotting, or feminine product collected with negligible observed MBL volume coupled with data indicating infrequent non-cyclic bleeding/spotting); the change from baseline to week 24 in uterine volume, the proportion of women who achieved a maximum Numerical Rating Scale

(NRS) score of ≤1 for UF associated with pain over the last 35 days of treatment in the subset of women with a maximum pain score of ≥4 during the 35 days before randomization (pain-evaluable population); and the incidence of treatment-emergent adverse events (AEs). Exploratory endpoints included change from baseline to week 24 in the BPD scale score. In addition, the change from baseline to week 24 in the Uterine Fibroid Symptom Quality of Life questionnaire (UFS-QoL) Symptom Severity (SS) scale score.

Statistical analyses

A mixed-effects model with an autoregression covariance structure was used for repeated measures (e.g., MBL volume). The mixed-effects model was used to estimate least square (LS) mean percentage change, with baseline MBL volume, treatment, visit, and treatment and visit interaction included as fixed effects. Analyses included baseline demographics across three cohorts and efficacy and safety endpoints. No statistical comparison was made between women with adenomyosis at baseline and the overall study population, and all assessments were descriptive.

RESULTS

A total of 770 women were randomized and treated in the LIBERTY 1/2 trials, with 610 (79.2%) women completing the pivotal studies. Of the 610 women who completed the study, 111 (18.2%) had a baseline diagnosis of adenomyosis, with 37 (18.3%) women in the relugolix combination therapy group, 45 (22.4%) women in the delayed group, and 29 (14.0%) in the placebo group (Table 1).

Baseline characteristics, body mass index, and MBL volume were similar across each treatment group in the adenomyosis population (Table 1). The most common major criteria observed were globular uterus and hyperechoic linear striations (observed in 97.3% and 71.2% of women, respectively) (Supplemental Table 1, available online). Myometrial cysts and hyperechoic islands were the two least observed major criteria (66.7% each). A heterogeneous uterus was the most observed minor criterion (93.7%). Translesional vascularity was the least observed minor criterion (0.9%). In this population of women with adenomyosis, 83.8% of the relugolix combination therapy group achieved both components of the compound primary efficacy endpoint compared with 80.0% in the delayed group and 27.6% in the placebo group (Fig. 1A). In total, 64.9% of women treated with relugolix combination therapy achieved amenorrhea over the last 35 days of treatment, compared with 68.9% of women in the delayed group and 6.9% in the placebo group (Fig. 1B).

By week 24, the LS mean uterine volume of women in the relugolix combination therapy, delayed, and placebo groups decreased by 22.2%, 24.4%, and 5.8%, respectively (Fig. 2A). The reported percent changes in MBL volume from baseline to week 24 were −85.3% (95% confidence interval [CI], −102.0 to −68.6), −91.7% (−107.1 to −76.4), and −34.6% (−53.1 to −16.1) in the relugolix combination therapy, delayed, and placebo groups, respectively (Fig. 2B).

Of the 37 women in the relugolix combination therapy group, 26 (70.2%) were defined as pain-evaluable patients, of which 11 (42.3%) achieved a maximum NRS score of ≤1 during the last 35 days of treatment (Supplemental Fig. 2). In the delayed group of 26/45 (57.8%) pain-evaluable patients, 10 (38.5%) women achieved the maximum NRS score of ≤1. In the placebo group of 19/29 (65.5%) pain-evaluable patients, 4 (21.1%) women achieved the maximum NRS score of ≤1. By week 24, a change from baseline in LS

TABLE 1

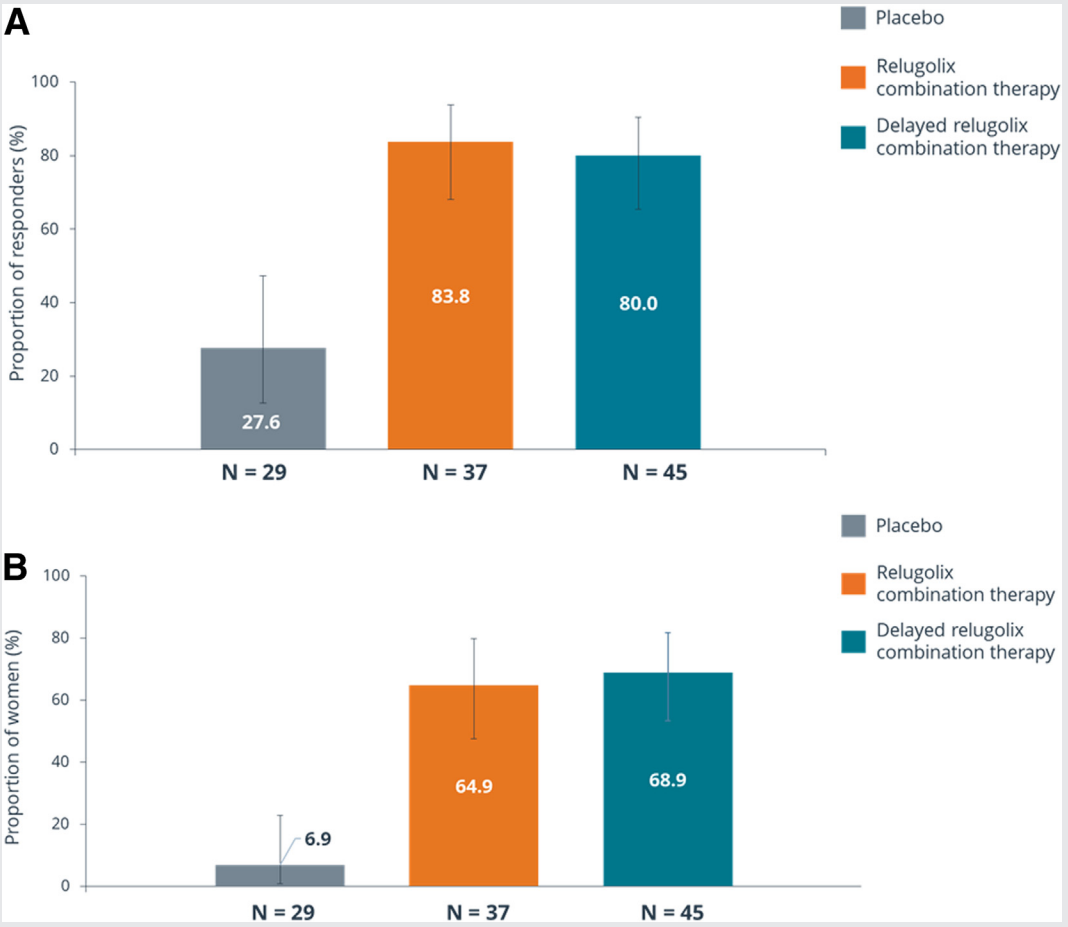
Demographics and baseline clinical characteristics of women with adenomyosis.

Demographics	Placebo N = 29	Relugolix combination therapy N = 37	Delayed relugolix combination therapy N = 45	Total N = 111
Age, mean (SD) years	42.5 (6.1)	44.2 (4.4)	42.2 (5.5)	42.9 (5.3)
Race, n (%)				
White	14 (48.3)	23 (62.2)	19 (42.2)	56 (50.5)
Black or African American	13 (44.8)	13 (35.1)	21 (46.7)	47 (42.3)
Asian	1 (3.4)	0 (0.0)	2 (4.4)	3 (2.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	3 (6.7)	3 (2.7)
Other	1 (3.4)	1 (2.7)	0 (0.0)	2 (1.8)
Body mass index, mean kg/m^2 (SD)	33.7 (8.4)	32.3 (5.9)	31.0 (4.8)	32.1 (6.3)
MBL volume, mean mL (SD)	229.9 (184.6)	256.3 (229.5)	216.6 (136.7)	233.3 (183.6)
Index UF volume, mean cm^3 (SD)	29.3 (37.3)	33.4 (60.9)	56.0 (147.3)	41.4 (101.7)
Uterine volume, mean cm^3 (SD)	258.4 (116.4)	281.6 (177.8)	351.5 (299.8)	303.9 (226.7)
Previous UF surgery, n (%)	2 (6.9)	2 (5.4)	6 (13.3)	10 (9.0)
History of prior pregnancy, n (%)	25 (86.2)	33 (89.2)	41 (91.1)	99 (89.2)

Note: SD = standard deviation; MBL = menstrual blood loss; UF = uterine fibroid.

Catherino. Relugolix combo therapy in adenomyosis. Fertil Steril 2025.

FIGURE 1



(**A**) Women with adenomyosis achieving an MBL volume <80 mL and a ≥50% reduction in MBL volume (treatment responders) from the pivotal study baseline to the last 35 days of treatment. [a]*P* value is based on the Cochran–Mantel–Haenszel test stratified by baseline MBL volume (<225 mL, ≥225 mL) and geographic region (North America, Rest of World). Error bars show upper and lower limits of 95% confidence intervals. (**B**) Proportion of women with adenomyosis who achieved amenorrhea over the last 35 days of treatment. Error bars show upper and lower limits of 95% confidence intervals. MBL = menstrual blood loss.

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mean BPD score of −59.0 (95% CI, −69.1 to −49.0) points in the relugolix combination therapy group was observed (Fig. 3A). Change in BPD score for the delayed and placebo groups was −58.5 (−68.1 to −48.8) and −21.1 (−32.6 to −9.7), respectively.

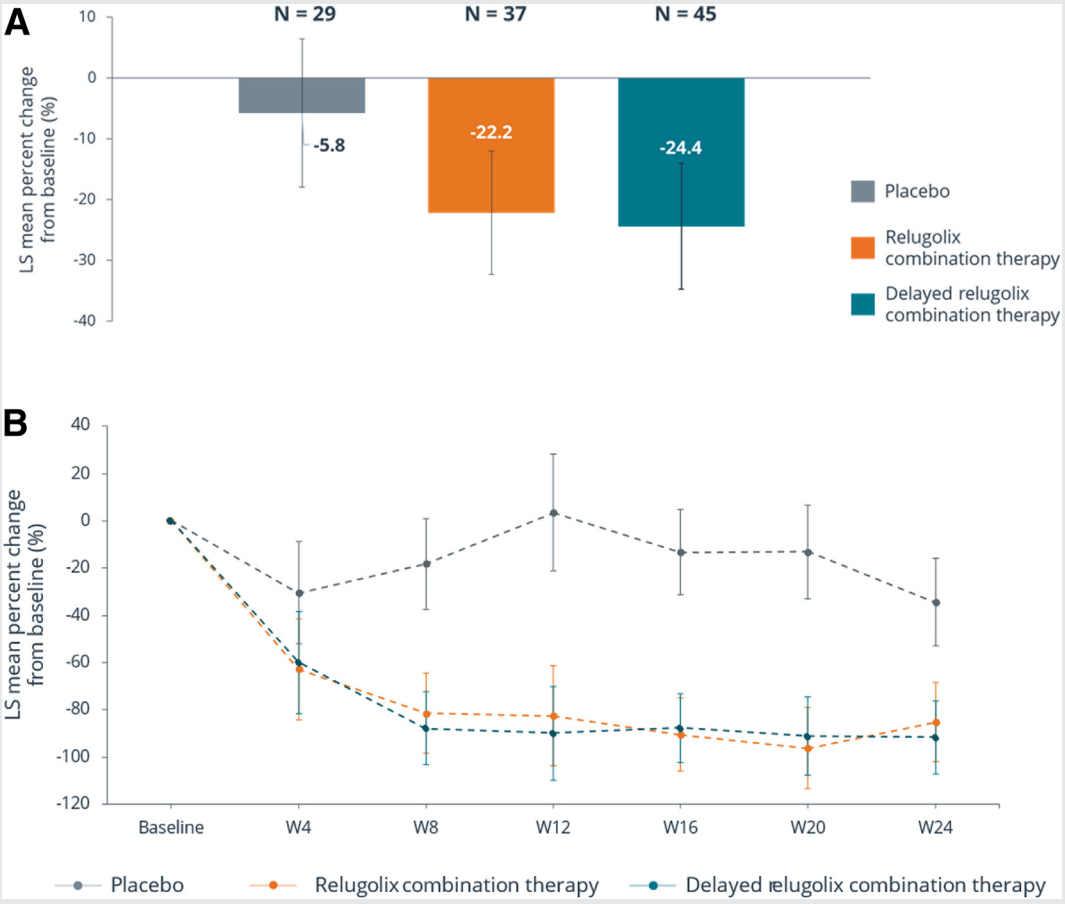
By week 24, a change from baseline in LS mean UFS-QoL SS scale score of −41.5 (95% CI, −50.4 to −32.7) points in the relugolix combination therapy group was observed (Fig. 3B). Change in UFS-QoL SS scale score for the delayed and placebo groups was −42.2 (−50.6 to −33.8) and −16.0 (−26.0 to −6.0), respectively.

In the adenomyosis subpopulation, AEs were reported in 20 (54.1%), 32 (71.1%), and 22 (75.9%) women in the relugolix combination therapy, delayed, and placebo groups, respectively (Supplemental Table 2, available online). Of these women, 3 (8.1%), 3 (6.7%), and 2 (6.9%) reported serious AEs (SAEs), respectively. Of the women in the relugolix combination therapy group, 1 (2.7%) woman reported an SAE related to treatment.

DISCUSSION

There is a lack of approved pharmacological options specifically indicated for the treatment of adenomyosis, presenting a clear unmet need in this population. Gonadotropin-releasing hormone receptor antagonists, which are indicated for the management of HMB associated with UF or moderate-to-severe pain associated with endometriosis, may be a potential option for the treatment of adenomyosis. Several studies have demonstrated the efficacy of GnRH antagonists in reducing uterine volume and managing symptoms in women with adenomyosis, suggesting potential as treatment options for long-term management (26–28). Data from other clinical trials conducted on women with UF and HMB suggest that the efficacy of relugolix with or without add-back estradiol and norethindrone acetate therapy is not decreased by coexisting adenomyosis (29). The

FIGURE 2



(**A**) Percent change in uterine volume of women with adenomyosis from baseline at week 24. Error bars show upper and lower limits of 95% confidence intervals. (**B**) Percent change in MBL volume of women with adenomyosis from baseline to the last 35 days of treatment. Error bars show upper and lower limits of 95% confidence intervals. LS = least square; MBL = menstrual blood loss; W = week.

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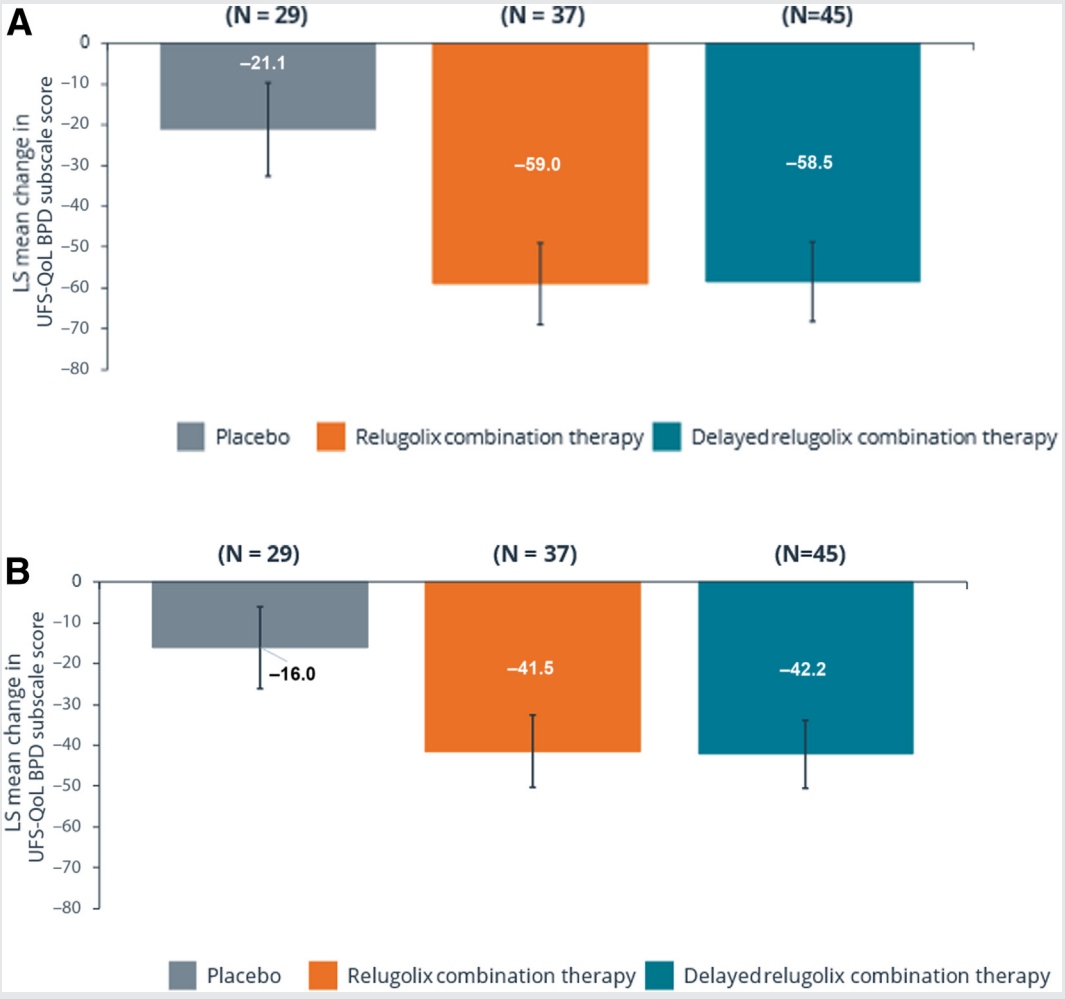
LIBERTY clinical trial program was designed to investigate the safety and efficacy of relugolix combination therapy in women with HMB-associated UF. Women with ultrasound features of adenomyosis were then identified in this post hoc analysis. Previous studies in women with UF have reported the prevalence of concomitant adenomyosis at screening to be between 20% and 34% (3, 13, 30). Similarly, in this analysis, 18.2% of LIBERTY 1/2 completers met the diagnostic criteria for adenomyosis, indicating that this population likely represents the broader population of women with UF and adenomyosis.

This analysis suggests that treatment outcomes, including reduction of HMB and MBL volume, observed in the overall LIBERTY 1/2 population were also demonstrated in the subgroup of women with adenomyosis at baseline (24). Although no statistical comparisons were performed between treatment arms or patients with adenomyosis and the overall study population, several trends were observed. At baseline, the mean index UF volume and uterine volume were lower in women with adenomyosis (41.41 cm^3 and 303.86 cm^3, respectively) compared with the baseline volumes in the relugolix combination therapy group in the overall LIBERTY 1/2 population (LIBERTY 1: 71.9 cm^3 and 379.1 cm^3, LIBERTY 2: 73.3 cm^3 and 387.7 cm^3) (24).

In the relugolix combination therapy group, the responder rate for an improvement in HMB for women with adenomyosis and UF (83.8%) was numerically higher than the overall LIBERTY 1/2 population (LIBERTY 1: 73%, LIBERTY 2: 71%). The percentage change in MBL volume by week 24 was similar (−85.3% in the adenomyosis population and −84.3% in the LIBERTY 1 and LIBERTY 2 populations) (24). Additionally, a greater proportion of women in the relugolix combination therapy arm were white (62%), as opposed to the placebo and delayed relugolix combination therapy arms (35% and 42%, respectively). However, in the overall LIBERTY study population, similar outcomes have been reported for Black/African American women treated with relugolix combination therapy (31).

FIGURE 3



(**A**) Change from baseline in UFS-QoL Bleeding and Pelvic Discomfort scale score in women with adenomyosis at baseline. Error bars show upper and lower limits of 95% confidence intervals. (**B**) Change from baseline in UFS-QoL Symptom Severity scale score in women with adenomyosis at baseline. Error bars show upper and lower limits of 95% confidence intervals. LS = least square; UFS-QoL BPD subscale = Uterine Fibroid Symptom Health-Related Quality of Life Bleeding and Pelvic Discomfort Subscale.

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Similar improvements in health-related quality of life, as measured by the change in UFS-QoL SS scale score, were observed in the relugolix combination therapy group in both the adenomyosis and overall LIBERTY 1/2 populations (25). Additionally, similar improvements in distress from key UF symptoms, as measured by the BPD subscale of the UFS-QoL scale, were observed in both of these populations (25). In the context of the LIBERTY clinical trial program, it should be noted that the definition of pain was associated with UF and not specifically or exclusively attributed to adenomyosis.

In the adenomyosis population, some minimal efficacy advantages were observed in the delayed group compared with the women who received relugolix combination therapy from baseline, such as a slightly greater proportion of women achieving amenorrhea (64.9% vs 68.9%). Similarly, efficacy advantages were also seen in the delayed treatment group of the overall LIBERTY 1/2 population (24). However, these minor improvements do not outweigh the hypoestrogenic effects observed in women treated initially with relugolix monotherapy, with a trend toward a higher proportion of women reporting hot flushes observed in the delayed group of both the adenomyosis population and the overall LIBERTY population (24). Furthermore, among women consistently treated with relugolix combination therapy for 24 weeks, the observed reduction in uterine volume was numerically greater in women with concomitant adenomyosis and UF as compared with the overall LIBERTY 1/2 population (22.2% in the adenomyosis population vs 12.9% in LIBERTY 1 and 13.8% in LIBERTY 2) (24). Current treatment options for adenomyosis are limited. Up to 82% of those affected with adenomyosis in the United States will

undergo definitive treatment with a hysterectomy (32). Uterine artery embolization for HMB associated with adenomyosis has shown failure rates as high as 50% over two years (32). Image-guided endometrial ablation techniques, such as high-intensity focused ultrasound, percutaneous microwave ablation, and radiofrequency ablation, have been used to improve HMB in patients with adenomyosis (33). Still, subsequent pregnancy is not recommended owing to substantial risks, including high rates of malpresentation, prematurity, placenta accreta, and perinatal mortality. Adenomyomectomy, an excisional procedure for adenomyosis, carries the risk of substantial morbidity in subsequent pregnancies: a high miscarriage rate, thinning of the uterine walls, and uterine ruptures in mid-to-late-pregnancy as well as a high incidence of placenta accreta and placenta percreta. Non-surgical options are generally perceived to be advantageous to patients with adenomyosis, with the levonorgestrel intrauterine system being the most researched for reducing HMB and pain, although mifepristone and dienogest have also shown effectiveness (34–37). Gonadotropin-releasing hormone antagonists have been demonstrated to improve symptoms, including in this post hoc analysis of the LIBERTY data. The reduction of uterine volume in women with adenomyosis through treatment with GnRH antagonists may result in improved fertility outcomes. However, a larger confirmatory study is required to establish definitive conclusions regarding fertility outcomes.

Treatment with relugolix combination therapy was well tolerated, with few SAEs reported over 24 weeks. The safety findings in the subgroup of women with adenomyosis were comparable with the overall LIBERTY 1/2 population, with a low rate of SAEs and a similar number of AEs and SAEs in the relugolix combination therapy and placebo groups (24).

Limitations of this study include the limited number of participants in the subgroup analyzed and the lack of stratification at enrollment by the presence of adenomyosis. However, randomization of participants at the start of the LIBERTY 1/2 trials should help address any potential for imbalances among treatment assignments at baseline. The diagnosis of disease in this population may be subject to bias, given that the diagnosis of adenomyosis was on the basis of retrospective evaluation of ultrasound images, rather than MRI images. Additionally, the baseline ultrasounds were not specifically performed to identify adenomyosis. As the adenomyosis population consisted of completers, it is possible that when comparing the data in this subpopulation with the overall LIBERTY population, the data could be perceived as being biased toward those patients who responded well to treatment with relugolix combination therapy and, therefore, completed the study. Baseline ultrasounds were not specifically performed to identify adenomyosis. However, a diagnostic algorithm was developed using features derived from MUSA diagnostic criteria, and a rigorous consensus guideline for central radiology readers was implemented to strengthen this post hoc evaluation (11, 38). In general, the adoption of ultrasound as a tool for the non-invasive diagnosis of adenomyosis is becoming increasingly common (11, 39). For patients seeking fertility or avoiding hysterectomy, transvaginal ultrasound allows for accurate diagnosis of adenomyosis, potentially leading to uterine preservation through surgical or pharmacological intervention (40). Although a combination of two or more ultrasound features has been shown to increase the specificity of this diagnostic tool (41), it should be noted that although ultrasound features of adenomyosis are different from those of UF, adenomyosis may be overlooked by the presence of large UF as shadowing may partially or completely obscure adenomyosis (42, 43); in this instance, MRI may be preferred as a more accurate diagnostic tool. Comparative assessment using MRI was beyond the scope of the LIBERTY studies. Despite this, transvaginal ultrasound is recommended for first-line imaging evaluation of the myometrium over MRI (10, 44).

CONCLUSION

In the subpopulation of women with concurrent UF and adenomyosis from the LIBERTY 1/2 trials, treatment with once-daily relugolix combination therapy was associated with a reduction in UF-associated HMB, uterine volume, severity of symptoms, and BPD scale scores, with an increase in the number of women experiencing minimal-to-no pain. The findings of this post hoc analysis indicate that there is no loss in effectiveness in the treatment of fibroids in women with adenomyosis and UF at baseline, treated with relugolix combination therapy, with comparable efficacy outcomes in this population, vs. the overall LIBERTY study population. As there are currently no approved medications available, relugolix combination therapy may be considered as an investigative therapeutic product in future studies for the potential medical management of women with both UF and adenomyosis.

CRediT Authorship Contribution Statement

William H. Catherino: Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Ayman Al-Hendy:** Writing – review & editing, Investigation, Conceptualization. **Souhil Zaim:** Writing – review & editing, Validation, Supervision, Software, Resources, Project administration, Methodology, Data curation, Conceptualization. **Nadia Bouzegaou:** Writing – review & editing, Validation, Methodology, Formal analysis. **Roberta Venturella:** Writing – review & editing, Methodology, Investigation. **Elizabeth A. Stewart:** Writing – review & editing, Conceptualization. **Rui Wu:** Writing – review & editing, Formal analysis. **Silvia Vannuccini:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Julie S. Perry:** Writing – review & editing, Writing – original draft, Data curation. **Viatcheslav G. Rakov:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Malcolm G. Munro:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Declaration of Interests

W.H.C. is a consultant to Sumitomo Pharma America, Bayer Pharma, and Pfizer. A.A.-H. is a consultant for AbbVie, Bayer, Novartis, ObsEva, Pfizer, and Sumitomo Pharma America;

had a research agreement with Crila; has research grants with the National Institutes of Health; and has several patents. S.Z. is an employee of Clario. N.B. has nothing to disclose. R.V. is a consultant for Sumitomo Pharma America. Over the last 36 months, E.A.S. has received grant/research financial support from the National Institutes for Health related to uterine fibroids (R01HD109127-01A1, and P50HD115283, P50HS023418) and adenomyosis (5R01HD105714); served as a consultant for AbbVie, Alnylam Pharmaceuticals, and Sumitomo Pharma America; holds a patent for Methods and Compounds for Treatment of Abnormal Uterine Bleeding (US Patent 6440445), which has no commercial activity; and has received royalties from UpToDate and payments for the development of educational content from the Med Learning Group, MED-IQ, Omnia, Physicians Educational Resources, and Web-MD; serves as an unpaid advisor to the Fibroid Foundation and the unpaid treasurer of the International Gynecologic Society. R.W. is a previous employee of Sumitomo Pharma America, Inc. S.V. has received consultancy fees from Gedeon Richter and Theramex. J.S.P. is a previous employee of Sumitomo Pharma America, Inc. V.G.R. is an employee of Sumitomo Pharma Switzerland GmbH. Over the past 36 months, M.G.M. has been a consultant for AbbVie Inc, Myovant Sciences Inc. (Sumitomo Pharma America, Inc.), Daiichi-Sankyo, Pharmacosmos, Hologic Inc, and Shield Therapeutics.

SUPPLEMENTAL MATERIAL

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