ORIGINAL ARTICLE

DOI: 10.52054/FVVO.2025.142
Facts Views Vis Obgyn 2025;17(3):245-252

Safety and efficacy of relugolix combination therapy in symptomatic uterine fibroids

Maria Chiara De Angelis[1], Fedora Ambrosetti[2], Sabrina Reppuccia[3], Fabiola Nardelli[3], Brunella Zizolfi[3], Antonella Mercurio[4], Antonio Maiorana[4], Attilio Di Spiezio Sardo[3]

[1]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy
[2]Department of Obstetrics and Gynaecology, APSS Trento, Santa Chiara Hospital, Trento, Italy
[3]Department of Public Health, School of Medicine, University of Naples Federico II, Naples, Italy
[4]HCU Obstetrics and Gynaecology, ARNAS Civico Di Cristina-Benfratelli Hospital, Palermo, Italy

ABSTRACT

Background: Relugolix-combination therapy (CT) (oestradiol 1 mg and norethindrone acetate 0.5 mg) is a new gonadotropin-releasing hormone antagonist licensed to treat heavy menstrual bleeding (HMB) associated with uterine fibroids; but little real-world data exists to guide practice.

Objectives: To evaluate the efficacy and safety of relugolix-CT in women with fibroid-associated HMB in two large Italian hospitals.

Methods: A retrospective multicentre study was conducted on 102 women with symptomatic fibroids and HMB, defined as a Pictorial Blood Assessment Chart (PBAC) score >100, who were treated with relugolix-CT for up to 24 months. Women were divided into three groups: group 1 (n=81) receiving only relugolix-CT treatment; group 2 (n=11) receiving at least two months of relugolix-CT prior to hysteroscopic, laparoscopic or open myomectomy; group 3 (n=10) receiving at least two months of pre- and post-myomectomy relugolix-CT.

Main Outcomes Measures: The primary outcome was resolution of HMB, defined as a PBAC score <100. Secondary outcomes included the side effects of treatment.

Results: The population mean age was 43.8 years (±6.06), and the mean baseline PBAC score was 329.9 (± 217 standard deviation). In women treated with relugolix-CT alone, 71 (94.7%) responded after two months. By nine months, only 36 (44.4%) women continued with relugolix-CT. Resolution of HMB was sustained in most women who continued treatment at each follow-up time point. By two months prior to myomectomy, HMB resolved in all women receiving relugolix-CT pre-surgery and nine (90%) women continuing relugolix-CT after myomectomy. No major side effects were reported.

Conclusions: This real-world study supports previous controlled trial data showing relugolix-CT to be a safe, efficacious medical treatment for HMB with fibroids.

What is New? Real-life clinical data support the use of relugolix-CT to treat symptomatic fibroids in isolation or combined with myomectomy.

Keywords: Gonadotropin-releasing hormone antagonist, heavy menstrual bleeding, relugolix, uterine fibroid, myomectomy

Corresponding Author: Maria Chiara De Angelis, MD, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy
E-mail: m.chiaradeangelis88@gmail.com **ORCID ID:** orcid.org/0000-0002-5817-2468
Received: 28.04.2025 **Accepted:** 20.09.2025 **Publication Date:** 30.09.2025

Cite this article as: De Angelis MC, Ambrosetti F, Reppuccia S, Nardelli F, Zizolfi B, Mercurio A, et al. A. Safety and efficacy of relugolix combination therapy for symptomatic uterine fibroids. Facts Views Vis Obgyn. 2025;17(3):245-252

Introduction

Uterine leiomyomas, also referred to as uterine "myomas" or "fibroids", are one of the most common benign, hormone-sensitive, uterine tumours with an estimated prevalence of 70-80% in premenopausal women.[1] When not asymptomatic, they account for symptoms that might severely affect patients' quality of life.[2] Heavy menstrual bleeding (HMB) is the most common symptom associated with fibroids, often leading to anaemia and other symptoms such as dysmenorrhoea, infertility and bulk, pressure effects.[2]

Surgery has long been the treatment of choice in women with fibroid-associated symptoms because medical options for fibroid-related symptoms can often be ineffective.[3] The recent development of oral gonadotropin-releasing hormone (GnRH) antagonists may finally provide an effective, fertility-sparing medical treatment for symptomatic uterine fibroids.[4] Relugolix is a GnRH antagonist, blocking the signalling of endogenous GnRH and thus leading to a fast and reversible suppression of ovarian function and oestradiol and progesterone production.[5] In order to minimise the side effects, mainly bone mineral density loss and vasomotor symptoms, an add-back therapy with oestradiol 1 mg and norethindrone acetate 0.5 mg has been formulated for a once-daily oral administration.[6]

The effectiveness and safety of once-daily relugolix-combination therapy (CT) has already been assessed in high-quality clinical trials.[7-9] However, these trials tend to select "less diseased" populations and, as a consequence, do not fully represent the "real life" context, as stated by Middelkoop et al.[10] in a recent systematic review. Therefore, the purpose of our study was to provide data on the efficacy and safety of relugolix-CT in women with fibroid-associated symptoms in a real-world clinical setting.

Methods

From June 2022 to September 2024, two Italian Hospitals (University of Naples and Public Hospital of Palermo) retrospectively collected data from electronic medical records of premenopausal women aged 18 years or older, diagnosed by ultrasound with at least one uterine fibroid; eligibility was subsequently confirmed through manual chart review according to the study criteria. Demographic and clinical information were entered into a dedicated de-identified database (in compliance with privacy requirements), including details regarding surgical procedures and subsequent follow-up.

Inclusion criteria comprised the presence of at least one uterine fibroid associated with HMB evaluated using the Pictorial Blood Assessment Chart scoring system (PBAC score >100), and a negative pregnancy test at screening. No patient had contraindications to hormonal therapy. All eligible patients received daily relugolix-CT (40 mg of relugolix, 1 mg of oestradiol, and 0.5 mg of norethindrone acetate).

We distinguished three subgroups as follows:

Group 1: Women who underwent only medical therapy.

Group 2: Women who underwent medical therapy before planned myomectomy.

Group 3: Women who received medical therapy before and after planned myomectomy.

All women underwent pelvic ultrasound to characterise fibroids according to the FIGO classification system[11], the Morphological Uterus Sonographic Assessment[12], and Lasmar classification.[13] Menstrual blood loss was assessed using the PBAC score before and during the therapy: a score higher than 100, corresponding to >80 mL of blood loss, was considered diagnostic for HMB, as described in the literature.[14,15] The primary outcome, resolution of HMB, was defined as a PBAC score <100 and further subcategorised: (i) full responder - amenorrhea and spotting only; (ii) bleeding (partial responder). A PBAC ≥100 was categorised as a non-responder. The main secondary outcome was side effects of relugolix-CT.

In Group 1 (relugolix-CT only), patients were followed at standardised intervals (at 1, 2, 3, 6, 9, and 12 months). Scheduled follow-up was conducted either in person or via telemedicine, uniformly across both centres. Additional contacts outside this schedule were arranged only when clinically necessary (e.g., for symptom management or reporting adverse events). In Group 2 (relugolix-CT pre-myomectomy), all patients underwent at least two months of therapy – during which data were collected – prior to undergoing hysteroscopic, laparoscopic, or laparotomic myomectomy, as had already been planned before initiation of therapy. In Group 3 (relugolix-CT pre and post myomectomy), all patients underwent at least two months of therapy – during which data were collected – prior to undergoing hysteroscopic or laparotomic

myomectomy. Due to the presence of a fibromatous uterus and/or additional myomas, and considering their perimenopausal status, medical therapy was continued postoperatively to prevent recurrence of bleeding. Patients were subsequently followed at 3 and 6 months after surgery.

An additional secondary outcome was to evaluate the feasibility of surgery and fibroid characteristics. These were evaluated during the surgical procedure on a numerical scales: fibroid vascularisation was rated from 1 to 5 (1: high, 2: moderate, 3: mild, 4: poor, 5: very poor); the ability to identify the cleavage plane was scored as 0 (easy) or 1 (difficult); fibroid consistency was graded on a scale from 0 (soft) to 10 (hard); and the difficulty of performing the surgical procedure was scored from 0 (very poor) to 10 (excellent), as previously reported.[16]

The study was conducted in accordance with the World Medical Association Declaration of Helsinki. All procedures complied with relevant laws and institutional guidelines and were approved by the Comitato Etico Campania 3 on August 7th, 2024 (report number: 12/24, registration number: 180/2024). Privacy rights of all participants were respected. Selected patients were contacted and signed informed consent forms (study participation and data privacy) prior to enrolment.

Statistical Analysis

In all three groups, given that all patients received at least two full months of relugolix-CT treatment, clinical and symptom-related variables were assessed and compared at baseline and after one and two months of therapy. For Group 1 (medical therapy only), additional assessments were conducted at 3-month intervals up to 24 months, depending on treatment continuation. Patients in Group 3 were re-evaluated at three and six months after surgery.

In the descriptive analysis, the continuous variables were summarised as mean and standard deviation (SD), while categorical variables were reported as absolute numbers and percentages. Statistical analysis was performed using the statistical package JMP Trial (v 17.2.0; JMP Statistical Discovery LLC). Continuous data are expressed as mean±SD.

Results

The final cohort consisted of 102 patients, retrospectively allocated as shown in Figure 1. Enrolled women presented with a mean age of 43.8 years (±6.06), ranging from 25 to 54 years of age, with 96 (94.1%) of Caucasic origin. Thirty-three patients (32.4%) had undergone a previous myomectomy, and 34 (33.3%) of patients had been treated with previous medical therapies. The mean PBAC

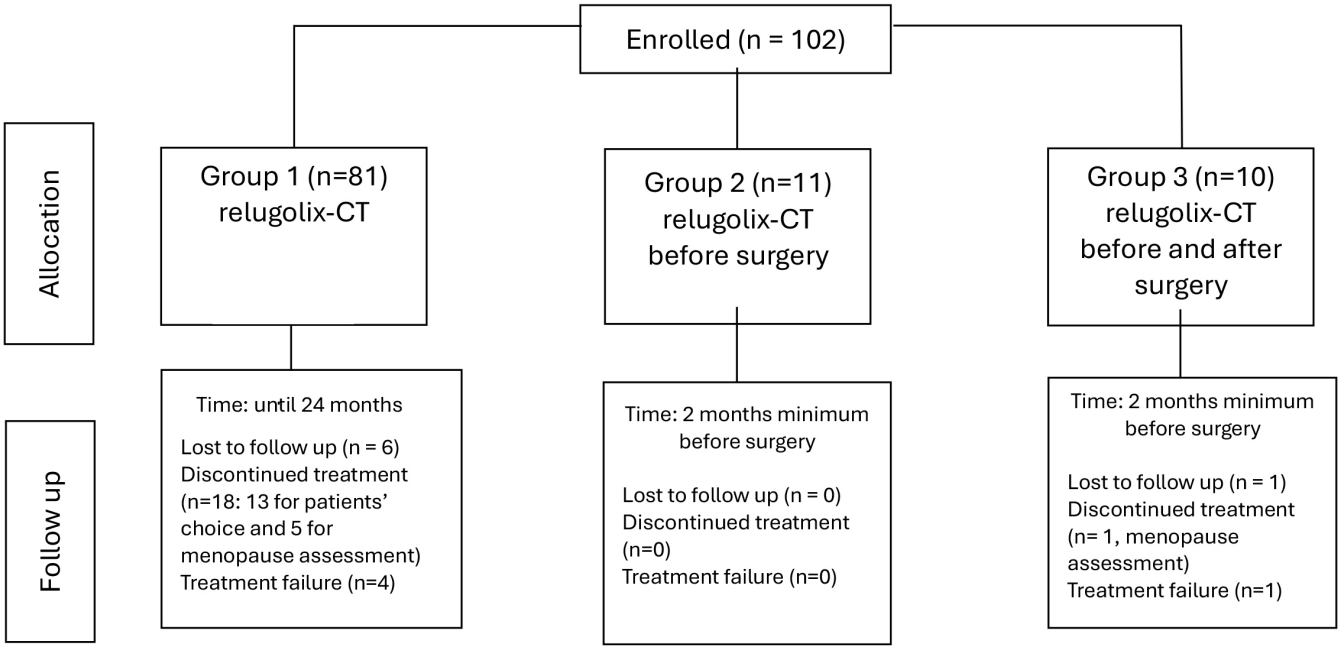

Figure 1. Study flow diagram.
CT: Combination therapy.

score before the introduction of relugolix CT treatment was 329.9 (SD±217; range 120 to 1400). Table 1 details the characteristics of included patients.

Women receiving medical therapy alone (Group 1) had their HMB symptoms resolved in 76 (93.8%) of women, with a full symptomatic response - reporting amenorrhea or only spotting - in 63 (77.8%) after one month of treatment. Due to dropouts and losses to follow-up, as well as the fact that patients started therapy at different times, the number of women who reached each specific follow-up time point varied accordingly (Table 1). Resolution rates remained stable from month three to two years for patients who continued treatment (Table 2).

In this relugolix-CT alone group, four women underwent hysterectomy: one was a non-responder (PBAC>100), and one discontinued treatment due to phlebitis-related complications. The remaining two patients achieved a partial therapeutic response (PBAC<100) after one and two months of therapy, respectively, but opted to discontinue daily medical treatment in favour of surgery.

All 11 patients in Group 2 received at least two full months of medical treatment with relugolix-CT before myomectomy. Regarding the HMB evaluation, at the end of the two-month treatment period, all women were full responders (Table 3). Myomectomy was performed by hysteroscopy in five women, by laparoscopy in two and by laparotomy in four women.

In Group 3, comprising 10 women who received relugolix-CT before and after surgery as part of a planned combined medical-surgical treatment approach, nine (90%) women had resolution of HMB, with six (60%) categorised as full responders (Table 2). Among women in this group, myomectomy was performed by hysteroscopy in 5 cases and by laparotomy in the remaining 5.

Regarding the surgical outcomes, in all patients scheduled for surgery (Group 2 and 3), the mean consistency of the fibroids after relugolix-CT pre-treatment was reported as 6.8/10 (SD±1.3), and the mean surgical difficulty was 4.7/10 (SD±1.4). The vascularisation of the fibroids was reported as mild or poor in 9 (42.9%) of women, and the cleavage plane was considered "easy" to identify in the majority of cases (20, 95.2%). No post-operative complications were reported.

In Group 3, which continued medical therapy after myomectomy, the evaluation of HMB at three months showed that three patients were partial responders (30%), while at six months, all patients were responders (100%).

In all women, the most frequent side effects of treatment were mild vasomotor symptoms, mild headache, mood swings, vaginal dryness, weight gain, or a sensation of fluid retention, as reported in previous studies (Table 4).

Table 1. Patients' characteristics at baseline.

PATIENTS' CHARACTERISTICS	
Age years	
mean±SD	43.80±6.06
min-max	25-54
Caucasian ethnicity	96/102 (94.1%)
BMI > 30	6/102 (5.9%)
Nulliparous	49/102 (48.0%)
Infertility	7/102 (6.9%)
Current smokers	18/102 (17.6%)
Previous failed therapy:	
-GnRH agonist	8/102 (7.8%)
-Ulipristal acetate	6/102 (5.9%)
-Combined oral contraceptive	20/102 (19.6%)
-Total	34/102 (33.3%)
Previous myomectomies	33/102 (32.4%)
Iron supplements	67/102 (65.7%)
PBAC score at baseline	
mean±SD	329.9±217
min-max	120-1400

SD: Standard deviation, BMI: Body mass index, GnRH: Gonadotropin-releasing hormone, PBAC: Pictorial blood loss assessment chart.

Discussion

Main Findings

Our data, investigating the efficacy and safety of relugolix-CT in real life, support this new drug as an effective long-term therapeutic resource in women with fibroid-associated symptoms, with a low risk of adverse events and complications. The use of relugolix CT may also help the feasibility of myomectomy, and HMB symptom recurrence is continued post-surgery. Side effects reported by our patients were mild and accounted mainly for vasomotor symptoms and headache, in a proportion which remained stable over the whole follow-up period. Similar records were also obtained by other studies[17], with no serious adverse events registered in our population.

Table 2. Heavy Menstrual Bleeding distribution in patients of Group 1.

Effect of relugolix-CT on heavy menstrual bleeding in women with fibroids receiving exclusive medical therapy (Group 1)									
	1 Month	**2 Months**	**3 Months**	**6 Months**	**9 Months**	**12 Months**	**15 Months**	**18 Months**	**21 Months**	**24 Months**
Relugolix-CT n (%)	81/81 (100)	75/81 (92.6)	64/81 (79.0)	49/81 (60.5)	36/81 (44.4)	26/81 (32.1)	17/81 (21.0)	10/81 (12.3)	6/81 (7.4)	4/81 (4.9)
Full responders (amenorrhea or spotting only) n (%)	63/81 (77.8)	65/75 (86.7)	54/64 (84.4)	40/49 (81.6)	33/36 (91.7)	23/26 (88.5)	15/17 (88.2)	10/10 (100)	6/6 (100)	4/4 (100)
Partial responders (PBAC<100) n (%) PBAC score mean±SD	13/81 (16.0) 81.0 (±8.8)	6/75 (8.0) 79.8 (±7.7)	3/64 (4.7) 88.3 (±3.4)	5/49 (10.2) 72.0 (±7)	3/36 (8.3) 89.0 (±5.2)	3/26 (11.5) 81.8 (±4)	2/17 (11.8) 78.0 (±1.5)	0	0	0
Non-responders (PBAC≥100) n (%) PBAC score mean±SD	5/81 (6.2) 190 (±52.2)	4/75 (5.3) 188.3 (±59.1)	7/64 (10.9) 193.4 (±68.3)	4/49 (8.2) 152.1 (±23.4)	0	0	0	0	0	0

PBAC: Pictorial blood loss assessment chart, SD: Standard deviation, CT: Combination therapy.

Strengths and Limitations

The focus on using relugolix-CT in everyday clinical and surgical needs represents the main strength of our study. We provided follow-up data out to two years and had a low rate of loss to follow-up. Limitations include the uncontrolled, observational and retrospective nature of our study, and the relatively small sample of patients.

Strengths and Limitations Compared to Other Studies

The demographic and clinical characteristics of our study population closely resemble those reported in previous European studies, as the one by Venturella et al.[7]: our patients were mainly non-smokers, non-obese white women in their 40s (43.8 years ± 6.06).

Regarding the history of medical therapy, we notice that most patients had experienced different treatments, but clearly, these could not fulfil women's needs and symptoms.

Compared with the recent publication by Al-Hendy et al.[18] on the treatment of symptomatic UFs with once-daily relugolix-CT, our study shows an even greater and more rapid reduction in HMB in a real-life setting. While the RCT reported a 60% reduction in HMB at one month, our medical-only group showed a reduction of 77.8% at the same time point. Moreover, the long-term effect on bleeding control is consistent with the registration trials.

Within the sample observed, 21 women were already planned for surgery independently of the pharmacological therapy: as recommended recently the choice of the approach should be shared in a common patient and healthcare point of view, considering the whole impact of UF and treatments on women's lives (clinical issues and therapeutic opportunities; women working life, sexual health and fertility).[19-23]

Table 3. Heavy Menstrual Bleeding distribution in patients of Groups 2 and 3.

Effect of preoperative relugolix-CT on heavy menstrual bleeding in women with fibroids undergoing myomectomy (Groups 2 and 3)				
	Group 2 relugolix-CT before surgery		**Group 3 relugolix-CT before and after surgery**	
	1 Month	**2 Months**	**1 Month**	**2 Months**
N. Pts in therapy	11	11	10	10
Full responders (amenorrhea or spotting only) n (%)	11/11 (100)	11/11 (100)	6/10 (60)	6/10 (60)
Partial responders (PBAC<100) n (%) PBAC score mean±SD	0	0	0	3/10 (30) 87.7 (±11)
Non-responders (PBAC ≥100) n (%) PBAC score mean±SD	0	0	4/10 (40) 152.5 (±60)	1/10 (10) 304.0

PBAC: Pictorial blood loss assessment chart, SD: Standard deviation, CT: Combination therapy.

The experience of this real-world retrospective study, where all women treated surgically underwent at least two months of preoperative therapy with relugolix-CT, shows that this medical treatment allows integration and maximisation of the synergy between medical and surgical approaches, supporting the concept that relugolix-CT can serve as an effective pre-operative therapy. This was evident in the clinical benefits observed regarding the evaluation of HMB, where only one non-responder was recorded, thus representing the only therapeutic failure. Moreover, the preoperative use of relugolix-CT improved the vascularisation and consistency of the fibroid, as well as the definition of the cleavage plane and the ease of surgical execution, as recorded by the surgeons, demonstrating that this pharmacological approach does not negatively affect the subsequent surgical procedure.

Few data are available on the surgical outcomes of GnRH antagonists' treatment[8], though they seemed promising to us, as compared to the previously available alternatives. A very recent observational study showed that preoperative GnRH-antagonist therapy may enhance haemoglobin levels, decrease uterine and fibroid size, and alleviate symptoms, potentially enabling safe surgical procedures[22].

Clinical and Policy Implications

Our study provides real-world data. It is well recognised that data from pivotal controlled trials to gain drug approvals may be derived from a "less diseased" population than will receive the treatments in the day-to-day clinical context.[10] Real-world evidence experiences are growing in recent years, providing helpful information that may complement randomised clinical trial findings and may help fill some gaps about the use in the real-world medical settings (larger samples, longer observational periods, more heterogeneous populations).[19] Our real-world evidence provides healthcare decision makers with clinical information about the impact of the drug on everyday life patients, adding beneficial value to public health.[20]

Unanswered Questions and Future Studies

In our record of cases, it was decided in a small percentage of cases to continue medical treatment after surgery to control the symptoms in case of remaining fibroids.

The benefits of continuing relugolix-CT post myomectomy to prevent recurrence of HMB and/or fibroids and future fertility (including outcomes of assisted reproductive techniques) need to be evaluated with further studies, ideally randomised controlled trials.)

Table 4. Side effects of relugolix-CT reported by patients. Values are expressed in numbers (%).

Side effects of relugolix-CT reported by patients										
	Follow-up visits									
	1 month	2 months	3 months	6 months	9 months	12 months	15 months	18 months	21 months	24 months
N. Pts in therapy	102	96	82	62	42	32	21	15	8	4
Side effects: n (%)										
- mild vasomotor symptoms	2 (1.9)	1 (1.0)	34 (41.5)	24 (38.7)	20 (47.6)	15 (46.9)	9 (42.9)	8 (53.3)	3 (37.5)	1 (25.0)
- mild headache	0	0	12 (14.6)	14 (22.6)	10 (23.8)	9 (28.1)	5 (23.4)	5 (33.3)	1 (12.5)	1 (25.0)
- mood swings	1 (0.9)	1 (1.0)	15 (18.3)	6 (9.7)	5 (11.9)	6 (18.8)	4 (19.0)	3 (20.0)	1 (12.5)	0
- vaginal dryness	0	0	11 (13.4)	7 (11.3)	3 (7.1)	2 (6.3)	1 (4.8)	0	0	0
- weight gain/fluid retention feeling	0	0	0	3 (4.8)	6 (14.3)	3 (9.4)	1 (4.8)	1 (6.7)	0	0
	1 (0.9)	0	5 (6.1)	3 (4.8)	3 (7.1)	1 (3.1)	1 (4.8)	1 (6.7)	0	0

CT: Combination therapy.

Acknowledgements: The Authors would like to thank the colleagues who provided precious technical help and the participants of our study for their invaluable time.

Contributors: Surgical and Medical Practices: M.C.D.A., A.Ma., A.D.S.S., Concept: M.C.D.A., A.M., A.Ma., A.D.S.S., Design: M.C.D.A., F.A., B.Z., A.M., A.Ma., A.D.S.S., Data Collection or Processing: M.C.D.A., F.A., S.R., F.N., B.Z., A.M., A.Ma., Analysis or Interpretation: M.C.D.A., F.A., S.R., F.N., B.Z., A.D.S.S., Literature Search: M.C.D.A., F.A., S.R., F.N., Writing: M.C.D.A., F.A., S.R., A.D.S.S.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests: All authors have completed the ICMJE Disclosure of Interest Form showing no competing interests.

Ethical approval: All procedures complied with relevant laws and institutional guidelines and were approved by the Comitato Etico Campania 3 on August 7th, 2024 (report number: 12/24, registration number: 180/2024).

Data sharing: Data supporting the results in the paper are archived in an appropriate public repository.

Transparency: The Authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG. 2017;124:1501-12.
2. Al-Hendy A, Myers ER, Stewart E. Uterine fibroids: burden and unmet medical need. Semin Reprod Med. 2017;35:473-80.
3. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003;188:100-7.
4. Syed YY. Relugolix/estradiol/norethisterone (norethindrone) acetate: a review in symptomatic uterine fibroids. Drugs. 2022;82:1549-56.
5. Barra F, Seca M, Della Corte L, Giampaolino P, Ferrero S. Relugolix for the treatment of uterine fibroids. Drugs Today (Barc). 2019;55:503-12.
6. Osuga Y, Enya K, Kudou K, Hoshiai H. Relugolix, a novel oral gonadotropin-releasing hormone antagonist, in the treatment of pain symptoms associated with uterine fibroids: a randomized, placebo-controlled, phase 3 study in Japanese women. Fertil Steril. 2019;112:922-9.
7. Venturella R, Rechberger T, Zatik J, Wagman RB, Zhu E, Rakov VG, et al. Relugolix combination therapy in European women with symptomatic uterine fibroids: a subgroup analysis from the randomized phase 3 LIBERTY pivotal trials. Gynecol Endocrinol. 2023;39:2249107.
8. Al-Hendy A, Venturella R, Arjona Ferreira JC, Li Y, Soulban G, Wagman RB, et al. LIBERTY randomized withdrawal study: relugolix combination therapy for heavy menstrual bleeding associated with uterine fibroids. Am J Obstet Gynecol. 2023;229:662.

9. Stewart EA, Lukes AS, Venturella R, Arjona Ferreira JC, Li Y, Hunsche E, et al. Relugolix combination therapy for uterine leiomyoma-associated pain in the LIBERTY randomized trials. Obstet Gynecol. 2022;139:1070-81.

10. Middelkoop MA, de Lange ME, Clark TJ, Mol BWJ, Bet PM, Huirne JAF, et al. Evaluation of marketing authorization and clinical implementation of ulipristal acetate for uterine fibroids. Hum Reprod. 2022;37:884-94.

11. Munro MG, Critchley HOD, Fraser IS; FIGO Menstrual Disorders Committee. The two FIGO systems for normal and abnormal uterine bleeding symptoms and classification of causes of abnormal uterine bleeding in the reproductive years: 2018 revisions. Int J Gynaecol Obstet. 2018;143:393-408.

12. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46:284-98.

13. Lasmar RB, Xinmei Z, Indman PD, Celeste RK, Di Spiezio Sardo A. Feasibility of a new system of classification of submucous myomas: a multicenter study. Fertil Steril. 2011;95:2073-7.

14. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynaecol. 1990;97:734-9.

15. Magnay JL, O'Brien S, Gerlinger C, Seitz C. Pictorial methods to assess heavy menstrual bleeding in research and clinical practice: a systematic literature review. BMC Womens Health. 2020;20:24.

16. Giarrè G, Franchini M, Castellacci E, Malune ME, Di Spiezio Sardo A, Saccone G, et al. Ulipristal acetate in symptomatic uterine fibroids. A real-world experience in a multicentric Italian study. Gynecol Endocrinol. 2020;36:171-4.

17. Al-Hendy A, Lukes AS, Poindexter AN 3rd, Venturella R, Villarroel C, McKain L, et al. Long-term relugolix combination therapy for symptomatic uterine leiomyomas. Obstet Gynecol. 2022;140:920-30.

18. Al-Hendy A, Lukes AS, Poindexter AN 3rd, Venturella R, Villarroel C, Critchley HOD, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med. 2021;384:630-42.

19. Trifirò G, Gini R, Barone-Adesi F, Beghi E, Cantarutti A, Capuano A, et al. The role of european healthcare databases for post-marketing drug effectiveness, safety and value evaluation: where does italy stand? Drug Saf. 2019;42:347-63.

20. Schad F, Thronicke A. Real-world evidence-current developments and perspectives. Int J Environ Res Public Health. 2022;19:10159.

21. Di Spiezio Sardo A, Ciccarone F, Muzii L, Scambia G, Vignali M. Use of oral GnRH antagonists combined therapy in the management of symptomatic uterine fibroids. Facts Views Vis Obgyn. 2023;15:29-33.

22. Muzii L, Galati G, Mercurio A, Olivieri C, Scarcella L, Azenkoud I, et al. Presurgical treatment of uterine myomas with the GnRH-antagonist relugolix in combination therapy: an observational study. Sci Rep. 2024;14:22481.

23. Di Spiezio Sardo A, Maiorana A, Muzii L, Scambia G, Venturella R, Vignali M, et al. It's time to make a change from a lesion-tailored to a patient-tailored approach in the management of uterine fibroids. Italian Journal of Gynaecology and Obstetrics. 2024;36:4–9.