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REVIEW ARTICLE

Considerations on implementation of the newest treatment for symptomatic uterine fibroids: Oral GnRH antagonists

Maria E. de Lange[1] | Annika Semmler[2,3] | T. Justin Clark[4] | Ben Willem J. Mol[5,6,7] | Pierre M. Bet[8] | Judith A. F. Huirne[2,3] | Wouter J. K. Hehenkamp[1,2]

[1]Department of Obstetrics and Gynaecology, Amsterdam UMC, location AMC, Amsterdam, The Netherlands

[2]Department of Obstetrics and Gynaecology, Amsterdam UMC, location Vrije Universteit MC, Amsterdam, The Netherlands

[3]Amsterdam Reproduction and Development Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

[4]Department of Obstetrics and Gynaecology, Birmingham Women's and Children's Hospital, Birmingham, UK

[5]Department of Obstetrics and Gynaecology, Monash University Monash Medical Centre, Clayton, Victoria, Australia

[6]Department of Obstetrics and Gynaecology, Aberdeen Centre for Women's Health Research, University of Aberdeen, Aberdeen, UK

[7]Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen, UK

[8]Department of Clinical Pharmacology and Pharmacy, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

Correspondence
Maria E. de Lange, Department of Obstetrics and Gynaecology, Amsterdam UMC, Location Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: m.e.delange@amsterdamumc.nl

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Abstract

Novel gonadotrophin releasing hormone (GnRH) antagonist treatments have recently been developed in combination with hormonal add-back therapy, as an oral treatment option for women suffering from uterine fibroids. Registration trials assessing the GnRH antagonist combination preparations with relugolix, elagolix and linzagolix have assessed treatment efficacy for fibroid-related heavy menstrual blood loss in comparison to placebo. Marketing authorization has been granted by several agencies including those in Europe, the United Kingdom and the United States. While the registration trials report a robust effect on the reduction of heavy menstrual blood loss and improvement in quality of life scores, reticence is advised before widespread prescription. In this review, we demonstrate limitations in the trial data, namely a lack of generalizability due to the restricted study population, the lack of transparency in the distribution of disease-level characteristics limiting the predictability of treatment success in the real-world diverse population, and the absence of any comparison to current alternative treatment methods. Importantly, no clinically meaningful volume reductions were found with GnRH antagonist combination preparations, and long-term safety data, particularly concerning modest but stable bone mineral density decline, need further addressing. Symptoms related to uterine fibroids adversely affect many women's quality of life and effective medical treatments are lacking. However, despite the urgent need for conservative treatments, it is vitally important that novel drugs, like combination oral GnRH antagonists, undergo sufficiently rigorous evaluation of safety, effectiveness and cost-effectiveness in a representative population and are compared with alternative treatment methods before introduction into mainstream clinical practice.

Maria E. de Lange and Annika Semmler are joint first authors.

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KEYWORDS
elagolix, fibroids, leiomyoma, linzagolix, oral GnRH antagonist, relugolix

1 | INTRODUCTION

Marketing authorization was granted in the United States (US) by the Food and Drug Administration (FDA) in May 2020 for **elagolix** combined with o**estradiol** and **norethisterone** acetate (Oriahnn®). This was the first combined preparation of an oral **GnRH antagonist** with add-back therapy introduced into clinical practice for treatment of uterine fibroid-associated symptoms. In May 2021 another comparable preparation, **relugolix** with oestradiol and norethisterone acetate (Myfembree®), was approved in the US for the same indication. The European Medicines Agency (EMA) as well as the Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom), and the Australian Register of Therapeutic Goods (ARTG) granted marketing authorization for an equivalent combination preparation with relugolix (Ryeqo®) in July 2021 and September 2022 respectively. **Linzagolix** (Yselty®) was the third oral GnRH antagonist to have been granted marketing authorization, in June 2022 by the EMA and the MHRA, albeit produced as a monotherapy in two dosages. Active marketing by the manufacturers is ongoing, advertising the combined oral GnRH antagonist with add-back therapy (GnRHant-ABT) as a long-term treatment option to replace other medical and surgical interventions. In the United Kingdom (UK), the manufacturer successfully applied for uptake of the relugolix combination therapy into the NICE guideline on heavy menstrual bleeding.

Uterine fibroids are very common, with a prevalence of up to 70% of women in the reproductive age group. Meanwhile, 25% of women with identified fibroids suffer from symptoms severe enough to necessitate treatment.[1] Patients with symptomatic uterine fibroids form a very heterogeneous group. Size, type and location of the fibroid(s), as well as the primary symptom and future fertility desires are important factors in the identification of optimal treatment options. Current treatments rely heavily on surgical procedures. While surgical treatments are expensive, with often long convalescence periods, risks of complications and a possible need for re-intervention, there is a great desire for long-term medical therapies that can replace invasive procedures.[2] As fibroid growth is oestrogen and progestogen dependent[3] the oral GnRH antagonist preparations form a promising potential to fulfil this treatment gap. However, careful introduction is warranted in order to identify which patients will benefit from this new treatment option and to prevent hasty implementation before cost-effectiveness has been proven.[4]

This opinion paper focuses on the recently introduced oral GnRH antagonist preparations that have been approved for long-term use for women with symptomatic fibroids. We will analyse the registration trials, discuss the current route for implementation and make recommendations for further evaluation prior to further implementation into routine clinical practice. There is an unmet need for an effective oral medical treatment for symptomatic fibroids. By advocating for more thorough evaluation of these novel medications we aim to promote more rational use of these pharmaceutical agents to optimize safety, effectiveness and cost-effectiveness.

2 | ORAL GNRH ANTAGONISTS

Development of oral GnRH antagonists commenced in 1989 and in 2002 the results of the first in vivo study in healthy postmenopausal women was published.[5,6] Pharmacotherapy with oral GnRH antagonists has been developed for the treatment of endometriosis, uterine fibroids and prostate cancer.[7–9] GnRH antagonists are selective, competitive GnRH receptor blockers, preventing the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, resulting in anovulation and subsequent amenorrhoea in a dose-dependent manner.[10,11] Both GnRH antagonists as well as GnRH agonists aim to reduce gonadotropin release and therefore oestrogen and progestogen release. Unlike GnRH agonists, GnRH antagonists do not induce an initial flare-up.[10] Blockage of the GnRH receptor, however, leads to a dose-dependent hypoestrogenic state and anovulation, with the risk of menopausal symptoms and reduction of bone mineral density (BMD). To alleviate these adverse effects, preparations combining the oral GnRH antagonists with hormonal replacement or add-back therapy (ABT) were created. Three oral GnRH antagonists have been registered for the treatment of uterine fibroids: relugolix, elagolix and linzagolix. To date, two combination preparations are registered (Table 1) for fibroid-related symptoms, containing either relugolix 40 mg or elagolix 300 mg, combined with oestradiol 1 mg and norethisterone acetate 0.5 mg. Their indications are either 'management of heavy menstrual bleeding associated with uterine leiomyomas in premenopausal women' (USA) or 'treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age' (Europe, UK, Australia).[12–14] Linzagolix has been authorized, as monotherapy in 100- or 200-mg tablet form, for the 'treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age'. In the instruction label, the addition of separate oral ABT with oestradiol 1 mg and norethisterone acetate 0.5 mg is suggested for both dosages when long-term treatment is foreseen.[15]

3 | WHAT IS KNOWN ABOUT ORAL GNRH ANTAGONISTS?

The phase 3 registration trials for relugolix-ABT, elagolix-ABT and linzagolix with and without ABT are outlined in Tables 2 and 3. For all preparations, two identical phase 3 randomized, double-blind,

TABLE 1 Oral GnRH antagonist preparations with marketing authorization for the treatment of symptomatic uterine fibroids.

GnRH antagonist (brand name)	Composition	Indication	Dosage	Regulatory agency approval	Manufacturer	Registration trials
Relugolix-ABT: Myfembree®	Tablet containing relugolix 40 mg, oestradiol 1 mg, norethisterone acetate 0·5 mg	Management of heavy menstrual bleeding associated with uterine leiomyomas in premenopausal women	One tablet once a day, for a maximum of 24 months	FDA: May 2021	Myovant Sciences	LIBERTY 1, 2
Relugolix-ABT: Ryeqo®	Film-coated tablet containing relugolix 40-, 1-mg oestradiol, and 0·5-mg norethisterone acetate	Treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age	One tablet once a day; no maximum duration stated	EMA: July 2021 MHRA: July 2021 ARTG: September 2022	Gedeon Richter	LIBERTY 1, 2
Elagolix-ABT: Oriahnn®	A treatment contains two types of capsules: 1. capsule with elagolix 300 mg, oestradiol 1 mg, norethisterone acetate 0·5 mg AND 2. capsule with elagolix 300 mg	Management of heavy menstrual bleeding associated with uterine leiomyomas in premenopausal women	One of each capsule once a day, for a maximum of 24 months	FDA: May 2020	AbbVie	Elaris UF-I, UF-II, Extend
Linzagolix: Yselty®	Two separate treatment dosages available as a film-coated tablet containing either (1) 100-mg linzagolix OR (2) 200-mg linzagolix	Treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age	(1) 100 or 200 mg once a day with ABT; no maximum duration stated (2) 100 mg daily without ABT; no maximum duration stated (3) 200 mg daily without ABT for <6 months	EMA: June 2022 MHRA: June 2022	Theramex (Kissei)	PRIMROSE 1, 2

Abbreviations: ABT, add-back therapy, added separately for linzagolix. Not part of the tablet; ARTG, Australian Register of Therapeutic Goods; FDA, Food and Drug Administration; MHRA, Medicines and Healthcare products Regulatory Agency; EMA, European Medicines Agency.

placebo-controlled, efficacy and safety studies were conducted with a total number of participants of 770, 791 and 1012 for the LIBERTY (relugolix), Elaris (elagolix) and PRIMROSE (linzagolix) trials, respectively. Premenopausal women >18 years were included, with an upper age limit of 50 (relugolix) or 51 (elagolix) years, and/or FSH level <35 or <20 U/L (linzagolix). The main inclusion criteria were the presence of heavy menstrual bleeding (defined as >80 mL per menstrual cycle as measured by the alkaline haematin method) as well as the presence of at least one fibroid with a diameter of at least 2 cm or multiple fibroids accumulating to a minimum uterine volume of 130 cm^3 (elagolix) or 200 cm^3 (linzagolix). All participants agreed to use a nonhormonal contraception method. Exclusion criteria included recent invasive fibroid treatment, a haemoglobin level <8 g/dL (5 mmol/L; relugolix and elagolix) or <6 g/DL (3,7 mmol/L; linzagolix) and having had a blood transfusion in the last 2 months in the relugolix and elagolix trials, as well as a uterine volume of greater than 2500 cm^3 in the elagolix trials. Candidates for the linzagolix trials were deemed ineligible if they had a uterine volume of greater than 20 weeks' gestation or 20-cm length from the cervix to fundus, or a single fibroid larger than 12 cm. In both the relugolix as well as the linzagolix trials, women were excluded from participation if their condition was likely to necessitate surgery for the fibroids. Other exclusion criteria included diagnosis or suspicion of (pre-)malignancy, history of or current venous and/or arterial thromboembolic event, history of osteoporosis or osteopaenia, abnormalities in clinical chemistry due to liver and/or renal impairment, 6-months post-pregnancy or abortion, (post)lactation, or cardiovascular disease. All trials were initiated and sponsored by pharmaceutical companies.

Figure 1 outlines these registration trials. In the LIBERTY (relugolix) trials, patients were randomized to treatment with relugolix-ABT for 24 weeks, monotherapy with relugolix 40 mg for the first 12 weeks followed by relugolix-ABT for the following 12 weeks or

TABLE 2 Baseline characteristics and outcomes of the LIBERTY and Elaris trials with a 24-week treatment.

		LIBERTY 1: Relugolix CT *vs* placebo[17]	LIBERTY 2: Relugolix CT *vs* placebo[17]	Elaris UF-1: Elagolix *vs* Elagolix CT vs placebo[18]	Elaris UF-2: Elagolix *vs* Elagolix CT vs placebo[18]
Design		Randomized, placebo-controlled, double-blind 24-week treatment	Randomized, placebo-controlled, double-blind 24-week treatment	Randomized, placebo-controlled, double-blind, double-dummy 24-week treatment	Randomized, placebo-controlled, double-blind, double-dummy 24-week treatment
Population		386 participants 49% Black, 45% White, 6% Other Africa, Europe, North/South America	381 participants 53% Black, 41% White, 6% Other Africa, Europe, North/South America	413 participants 68% Black, 28% White, 4% Other USA (including Puerto Rico)	378 participants 67% Black, 31% White, 2% Other USA (including Puerto Rico)
Baseline characteristics	Age (mean)	42 years	42 years	42 years	42 years
	Menstrual blood loss/cycle (mean ± SD)	228 mL ± 155	229 ± 150	247 mL ± 165	236 mL ± 158
	Fibroid volume (largest fibroid) mean ± SD mean diameter[b]	79 cm^3 ± 132 5.3 cm	76 cm^3 ± 136 5.2 cm	66 cm^3 ± 113 5.0 cm	76 cm^3 ± 136 5.3 cm
	Uterine volume (mean volume ± SD)	416 cm^3 ± 357	399 cm^3 ± 372	484 cm^3 ± 394	527 cm^3 ± 452
	UFS-QoL SS (mean score)	59 pts	60 pts	60 pts	62 pts
	UFS-QoL HrQol (mean score)	37 pts	37 pts	42 pts	43 pts
Intervention (no.)		RGX-ABT (128) RGX-delayed ABT (132)	RGX-ABT (125) RGX-delayed ABT (127)	EGX-ABT (206) EGX (104)	EGX-ABT (189) EGX (95)
Comparison (no.)		Placebo (127)	Placebo (129)	Placebo (102)	Placebo (94)
Primary outcome	% Women with a control of menstrual blood loss[a]	RGX-ABT: 71%–73%[c]	P: 15%–19%	EGX-ABT: 69%–77%[c]	P: 9%–10%
Secondary outcomes	% Women with amenorrhoea in the last treatment month	RGX-ABT: 50%–52%[c]	P: 3%–6%	EGX-ABT: 48%–53%[c]	P: 4%–5%
	Fibroid volume (% change from baseline)	RGX-ABT: −12% to −17%	P: −7% to 0%	EGX-ABT: −1% to −6%∼	P: −2% to 15%∼
	Uterine volume (% change from baseline)	RGX-ABT: −13% to −14%[c]	P: −1.5% to 2%	EGX-ABT: −5% to 1%∼	P: 9% to 11%∼
	UFS-QoL (Score change from baseline) SS	RGX-ABT: −35 pts[c]	P: −13 pts	EGX-ABT: −33 to −41 pts[c]	P: −8 to −10pts
	UFS-QoL (Score change from baseline) HrQoL	RGX-ABT: +38 pts[c]	P: +13 pts	EGX-ABT: +38 to 42 pts[c]	P: +6 to +11 pts
Safety	AEs (% participants with AE)	RGX-ABT: 60%–62%	P: 59%–66%	EGX-ABT: 68%	P: 70%

(Continues)

TABLE 2 (Continued)

	LIBERTY 1: Relugolix CT *vs* placebo[17]	LIBERTY 2: Relugolix CT *vs* placebo[17]	Elaris UF-1: Elagolix *vs* Elagolix CT *vs* placebo[18]	Elaris UF-2: Elagolix *vs* Elagolix CT *vs* placebo[18]
Bone mineral density (% change from baseline in lumbar spine)	RGX-ABT: −0%·1 to −0.4%	P: +0·1 to 0·3	EGX-ABT: −0.6% to −0.8%	P: −0·1% to −0·2%
Lipid levels	No meaningful differences across groups		Mean increase in total cholesterol, LDL, HDL, TG in EGX-ABT	
Liver levels	No. of women with ALT/AST ≥ 3× ULN: 2:1 (RGX-ABT: P)		No. of women with ALT/AST ≥ 3× ULN: 6:0 (EGX-ABT: P)	
Dropout rate (total/due to AE)	RGX-ABT: 18%–22%/2%–6%	P: 17%–21%/4%–5%	EGX-ABT: 20%–22% /8%	P: 19%–28% / 3%–7%

Note: Dark blue highlighted preparations indicate that these preparations have been approved for market authorization. For the baseline characteristics, an average of the mean and SD was calculated from the three different intervention arms. For the results, a range is given representing the mean of trial 1 and of trial 2. Results of GnRH antagonist monotherapy are not shown.

Abbreviations: AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGX-ABT, elagolix 300 mg – elagolix 300 mg/40 mg/oestradiol 1 mg/norethisteronacetate 0.5 mg; HrQoL, Health-related Quality of Life score range 0–100. Higher scale indicates better quality of life. *These scores were not reported in the primary study, were based on subgroup of participants (N = 582), and published in EMA*.[16]; P, Placebo; RGX-ABT, relugolix 40 mg/estradiol 1 mg /norethisteronacetate 0·5 mg; SS, Symptom Severity Score range 0–100, higher scale indicates increased symptom severity; UFS-QoL, The Uterine Fibroid Symptom and Quality of Life Questionnaire; ULN, upper limit normal.

[a]Control of menstrual blood loss defined as <80 mL per menstruation and a reduction of 50% from baseline.

[b]Mean volume calculated from the mean volume in each treatment group. Mean diameter calculated from volume. Formula used: $V = 4/3 \times \pi \times r^3$.

[c]Statistically significant compared to placebo; ~ indicates that values had to be estimated from the published figures.

placebo for 24 weeks. The registration trials for elagolix, Elaris UF-1 and UF-2, had a similar design, with the exception that the monotherapy group continued on monotherapy throughout the 24 weeks. In contrast, the PRIMROSE (linzagolix) trials randomized patients into a group treated with 100-mg linzagolix monotherapy, 100-mg linzagolix-ABT, 200-mg linzagolix monotherapy, 200-mg linzagolix-ABT for 24 weeks or placebo for 24 weeks.[17–19] All trials assessed prolonged treatment of up to 52 weeks with extension trials. The relugolix and elagolix trials continued with open-label extension trials, for which participants were eligible if they had a menstrual blood loss reduction according to the primary outcome criteria, and treatment did not result in a 7%–8% BMD reduction (see Figure 1).[16,19,20] Only outcomes of GnRHant treatment with regulatory approval, with a possible treatment duration of up to 2 years and beyond, will be reported here.

3.1 | Efficacy outcomes with a 24-week treatment period

The primary efficacy endpoint for the registration trials was control of menstrual blood loss defined as <80 mL per menstruation and a reduction of 50% from baseline at week 24. Participants reaching this endpoint were referred to as responders. Secondary efficacy endpoints included change in fibroid and uterine volume, haemoglobin levels, and quality of life as measured by the Uterine Fibroid Symptom and Quality of Life questionnaire (UFS-QoL). Key baseline characteristics and outcomes are presented in Tables 2 and 3.

The registration trials revealed that GnRH antagonists with or without ABT can significantly reduce menstrual blood loss when compared to placebo after 24 weeks of treatment. For relugolix-ABT and elagolix-ABT, up to 77% of participants were classed as responders at the end of their treatment *vs*. 9%–19% in the placebo group. In the final treatment month, an amenorrhoea rate was 48%–53% of women receiving treatment *vs*. 3%–6% in the placebo group. Treatment with the linzagolix preparations had similar results, with 66%–78% responders for linzagolix 100 mg with ABT. Linzagolix 200 mg with ABT had the best result with 76% up to 94% responders, whereas linzagolix 100 mg without ABT, with 57%, had the lowest response rate. Amenorrhoea rates were also lowest at 34%–38% for linzagolix 100 mg without ABT and highest for linzagolix 200 mg with ABT, at 58%–81%. With all treatments, patients reported improvements in quality of life as measured by Symptom Severity and Health-related Quality of Life questionnaires. After a 24-week treatment period, there was no statistically significant volume reduction of the largest fibroid with the use of either relugolix-ABT or elagolix-ABT. For uterine volume reduction, relugolix-ABT resulted in a statistically significant mean reduction of around 14% (an average diameter reduction from 9.1 to 8.7 cm). Elagolix-ABT did not show a significant uterine volume reduction on pelvic ultrasound measurements.[17–19] In the linzagolix trials, fibroid volume was a cumulative measurement of the three largest fibroids. For linzagolix-ABT 200 mg, only the PRIMROSE 2 trial reported a statistically significant fibroid reduction of 21%.

TABLE 3 Baseline characteristics and outcomes of the PRIMROSE trials with a 24-week treatment.

			PRIMROSE 1: Linzagolix *vs* linzagolix-ABT *vs.* placebo[19]		PRIMROSE 2 Linzagolix *vs* linzagolix-ABT *vs.* placebo[19]	
Design			Randomized, placebo-controlled, doubled-blind 24 weeks with 28-week extension		Randomized, placebo-controlled, doubled-blind 24 weeks with 28-week extension	
Population			511 participants 63% Black, 33% White, 4% Other USA		501 participants 5% Black, 95% White Europe and USA	
Baseline characteristics	Age (mean)		42 years		43 years	
	Menstrual blood loss/cycle (mean)		198 mL		216 mL	
	Total fibroid volume of 3 largest fibroids median volume (IQR) median diameter[b]		60 cm^3 (21–140) 4.8 cm		50 cm^3 (23–114) 4.6 cm	
	Uterine volume (median (IQR))		297 cm^3 (192–496)		203 cm^3 (139–308)	
	UFS-QoL SS (mean score)		63 pts		52 pts	
	UFS-QoL HrQol (mean score)		36 pts		45 pts	
Study arm (no.)	PRIMROSE 1	Placebo (103)	LGX 100 mg (94)	LGX-ABT 100 mg (107)	LGX 200 mg (105)	LGX-ABT 200 mg (103)
	PRIMROSE 2	Placebo (102)	LGX 100 mg (97)	LGX-ABT 100 mg (101)	LGX 200 mg (103)	LGX-ABT 200 mg (98)
Primary outcome	% Women with a control of menstrual blood loss[a]	29%–35%	56%–57%[c]	66%–77%[c]	71%–78%[c]	76%–94%[c]
Secondary outcomes	% Women with amenorrhoea in the last treatment month	12%–21%	34%–38%[c]	42%–63%[c]	60%–71%[c]	58%–81%[c]
	Fibroid volume (% change from baseline)	−5% to 4%	−16% to −25%	−7% to −2%	−44% to −49%[c]	−13% to −21%
	Uterine volume (% change from baseline)	2%–6%	−15% to −17%[c]	−12% to 6%	−31% to −43%[c]	−8% to −20%
	UFS-QoL (Score change from baseline) SS	−12 to 13 pts	−20 to −25pts[c]	−26 to 35 pts[c]	−32 to −37 pts[c]	−33 to −35 pts[c]
	UFS-QoL (Score change from baseline) HrQoL	+10 to 16 pts[c]	+20 to 26 pts[c]	+ 23 to 37 pts[c]	+30 to 35 pts[c]	+31 to 34 pts[c]

(Continues)

TABLE 3 (Continued)

Safety	AEs (% participants with AE)	54 to 45%	50 to 65%	45 to 62%	62 to 71%	52 to 63%
	Bone mineral density (% change from baseline in lumbar spine)	24 weeks: +0.4 to +0.5% 52 weeks (PRIMROSE 1): −0.9%	24 weeks: −2.0% to −2.1% 52 weeks: −2.2% to −2.4%	24 weeks: −0.8% to −1.4% 52 weeks: 0% to −1.5%	24 weeks: −3.3% to −4.1%	24 weeks: −0.8% to −1.4% 52 weeks: −0.9% to −2.0%
	Lipid levels	• Small increases in lipids, highest in participants with LGX 200 mg				
	Liver levels	• A dose-dependent increase in aminotransferases was seen which were reversible and not paired with increased bilirubin or alkaline phosphatase				
	Dropout rate (total/due to AE)	11%–36% /3%–6%	18%–31% /3%–6%	20%–38%/4%–7%	15%–26%/8%	13%–30%/2%–6%

Note: Dark blue highlighted preparations indicate preparation with marketing authorization for long-term treatment. If available, information about the mean/median from the baseline characteristics were extracted from Donnez et al.[19] or EMA.[33] If not, the average from the different intervention arms was taken. For the results, a range is given representing the mean of trial 1 and of trial 2.
Abbreviations: ABT, add-back therapy added through a separate tablet; AE, adverse events; ALT, alanine aminotransferase; AST, aspartate-aminotransferase; HrQoL, Health-related Quality of Life score range 0–100. Higher scale indicates better quality of life; LGX, Linzagolix; P, Placebo; SS, Symptom Severity Score range 0–100, higher scale indicates increased symptom severity; UFS-QoL, The Uterine Fibroid Symptom and Quality of Life Questionnaire; ULN, upper limit normal.
[a]Control of menstrual blood loss defined as <80 mL per menstruation and a reduction of 50% from baseline.
[b]Mean volume calculated from the mean volume in each treatment group. Mean diameter calculated from volume. Formula used: $V = 4/3 \times \pi \times r^3$.
[c]Statistically significant compared to placebo; Significance only shown if outcomes in both trials PRIMROSE 1 and 2 are statistically significant.

PRIMROSE 1 reported no such reduction. Similarly, only in PRIMROSE 2 were uterine volume reductions of 12% and 20% observed for Linzagolix-ABT 100 mg and Linzagolix-ABT 200 mg, respectively. Only linzagolix 100-mg monotherapy gave a consistent reduction in uterine volume of up to 17% in both trials (an average diameter reduction from 8.6 to 8.1 cm).[19]

3.2 | Safety outcomes with a 24-week treatment period

The most common adverse reactions seen with GnRH antagonists were hot flushes. These were reported in 6%–11% of the relugolix-ABT group, 20% of the elagolix-ABT group, and 3%–13% of the linzagolix-ABT groups *vs.* 4%–9% in the placebo groups. After 24 weeks, the results on BMD indicated an overall small reduction in all the GnRHant-ABT groups (−0.1% to −1.4%; see Tables 2 and 3). Linzagolix 100-mg monotherapy resulted in BMD reductions of up to −2.1%. No incidences of drug-induced liver injury or clinically significant endometrial abnormalities were found. While there were no increases in lipid levels with relugolix-ABT, with elagolix-ABT treatment, transient increases in lipid levels, particularly total cholesterol (13–17-point increase) and LDL cholesterol (10–14-point increase), were reported, which plateaued after the first 3 month of treatment.[17,18] Linzagolix with or without ABT also showed small increases in lipids, particularly in the linzagolix 200-mg group. Total cholesterol increased up to 15% while LDL cholesterol increased up to 20%. Moreover, there was a dose-dependent increase in aminotransferases with linzagolix which plateaued with continued treatment up until 52 weeks. The highest increase was seen in linzagolix 100 mg with a mean change of up to 5 points.[19] Overall discontinuation rates were similar across treatment groups and comparable to the placebo groups, ranging around 20%. Adverse events, not further specified, accounted for 2%–8% of discontinuations in the trials. Participants of the PRIMROSE (linzagolix) 1 trial across all groups, including placebo, had a higher discontinuation rate ranging from 26% to 36% as compared to the other studies (see Tables 2 and 3).

3.3 | Efficacy and safety outcomes with a 52-week treatment period

To assess a prolonged treatment efficacy, the relugolix-ABT and elagolix-ABT trials continued an open-label extension trial for another 24–28 weeks (a total treatment duration of 52 weeks) for which participants were eligible if they were responders without significant BMD reduction. For relugolix-ABT, 47% ($n = 363$) of women initially treated with relugolix-ABT completed the 52-week treatment course. For elagolix-ABT, this was 46% ($n = 182$).[16,20,21] Participants in the linzagolix trials receiving linzagolix 100 mg, linzagolix-ABT 100 mg and linzagolix-ABT 200 mg continued treatment for up to 52-weeks with completion rates ranging from 36%–47% ($n = 39$–45) to 67%–70% ($n = 56$–72) in PRIMROSE 1 and 2 respectively.[19] The

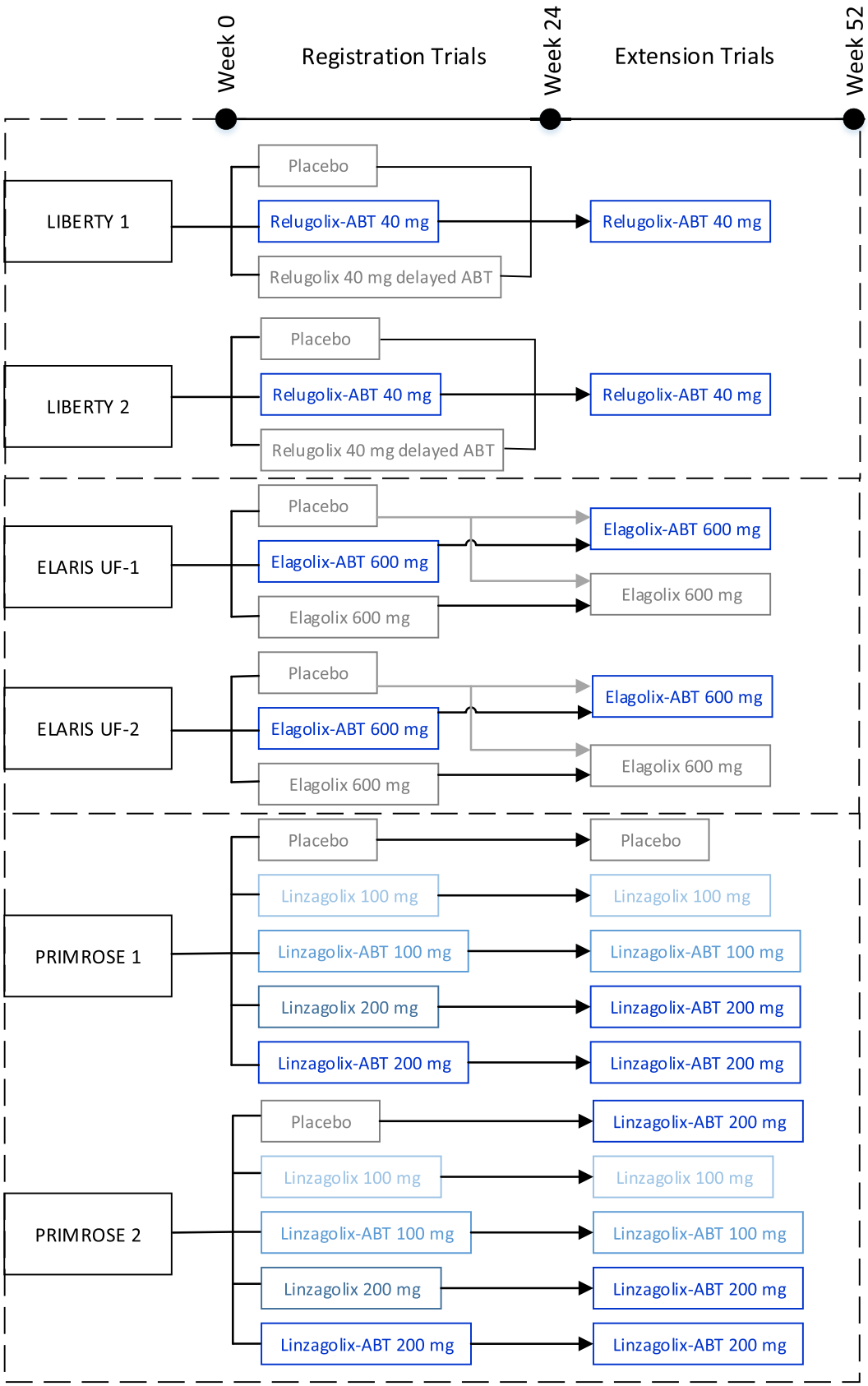

FIGURE 1 GnRH antagonist preparations registration and extension trials. All preparations in blue have received marketing authorization for treatment of uterine fibroids. The extension trials of LIBERTY and ELARIS were open-label trials for which women were eligible if they had met the primary outcome criteria and did not have a bone mineral density loss of 7–8%. ABT = oestradiol 1 mg, norethisteronacetate 0.5 mg.

abovementioned trials report that, amongst the women entering the extension trials, the effect of oral GnRHant treatments remain stable concerning the amount of menstrual blood loss when treatment continued to 52 weeks. Similarly, amenorrhoea rates, anaemia and quality of life scores remained improved. Regarding uterine and fibroid volume, this was not reported upon for the relugolix-ABT extension trial. In the elagolix-ABT extension trial, fibroid volume remained unchanged while uterine volume reduced by 12% compared to the initial baseline, translating to a reduction in diameter from 9.7 to 9.3 cm. For linzagolix-ABT and linzagolix 100 mg monotherapy, uterine and fibroid volumes did not further decrease with continued treatment after 24 weeks.[19] Adverse effects did not significantly increase with treatment up to 52 weeks. A further decline in BMD from baseline was observed after 52 weeks of treatment with −0.8% for relugolix-ABT, −1.5% for elagolix-ABT, up to −1.5% on average for linzagolix-ABT 100 mg, and up to −2% on average for linzagolix-ABT 200 mg as compared to 24 weeks of treatment.[19–21]

4 | PREMARKETING REGISTRATION OF A NEW DRUG

In order to obtain marketing authorization for a medical treatment, pharmaceutical companies must assure its efficacy, safety and quality through well-designed studies generating robust data. The EMA has produced a set of questions to assess whether a study is adequately designed prior to marketing authorization.[22]

- Was the appropriate (target) population studied?
- Were the studied outcomes relevant?
- Was a comparison to an appropriate alternative treatment made?
- Will long-term safety outcomes be adequately collected?

By addressing each of these items of this framework for the oral GnRHant preparations, we aim to identify what is known and what possible knowledge gaps exist, enabling an assessment of their place amongst the therapeutic options for symptomatic fibroids.

4.1 | Ad 1. An appropriate patient population

To make trial outcomes relevant and generalizable to the whole patient population, studies should include an ethnically diverse population, as well as participants throughout the reproductive age range, with fibroids varying in size, number and location, and who suffer from significant symptoms as identified through semi-objective measures.[23,24] Black and Asian women have a higher incidence of uterine fibroids, with often more severe symptoms and possibly a different response to treatment.[25]

In the oral GnRHant trials, the age range was broad in all trials (95% range was ~31–54 years of age). In terms of race, 49–68% of participants were registered as Black, except in the PRIMROSE 2 trial, with 5% Black participants. The number of participants of Asian descent was not specified (see Tables 2 and 3). All participants had at least one fibroid of 2-cm diameter, or multiple fibroids with a minimum uterine volume of 130 cm^3 for the relugolix-ABT trials and 200 cm^3 for the elagolix-ABT and linzagolix trials. The elagolix-ABT and linzagolix trials excluded women with significantly large uteri, as well as fibroids larger than 12 cm for the linzagolix trials. From the baseline characteristics it can be deducted that the majority of participants had a fibroid smaller than 5 cm in diameter. For the linzagolix trials, the median diameter of the three largest fibroids was 4.6–4.8 cm. Information on the type (FIGO classification), location, number and more detailed information on the size of the fibroids was not available in any of the studies. Symptoms were significant and objectified through the alkaline haematin method for heavy menstrual bleeding[26] and UFS-QoL questionnaire for fibroid-related symptoms.[27] The average menstrual blood loss at baseline across trials was around 225 mL. Symptom severity and Health-Related Quality of Life, as measured by the UFS-QoL questionnaire, revealed moderate symptom severity and an important impact on quality of life by uterine fibroids in all trial populations.[28] In the relugolix-ABT and elagolix-ABT trials, women with moderate anaemia and recent blood transfusion and in the linzagolix trials, women with severe anaemia, were not eligible to participate. In the relugolix-ABT and linzagolix trials, women with symptoms that likely required surgery in the future were also not deemed eligible to participate.[17,18] For the treatment duration up to 52 weeks, participant selection took place in the relugolix and elagolix extension trials, as nonresponders and participants with more than 7%–8% loss of BMD were excluded. No criteria are mentioned for inclusion in the extension trial of up to 52 weeks within the linzagolix trials. During treatment, all participants were requested to use nonhormonal contraception if sexually active.[16,19,20]

4.2 | Ad 2. Relevant outcomes

Relevant outcomes of fibroid treatments include impact on symptoms, such as amount of blood loss, pain or bulk pressure symptoms, as well as impact on fibroid and uterine volume, expected time to optimal treatment effect, and the sustainability of the treatment effect. Side effects and adverse events in terms of safety are of relevance, as well as impact on fertility and pregnancy outcomes. Which outcome is most relevant depends on individual patient variables, i.e. which symptom is most burdensome, but also whether or not a future pregnancy is still desired.

In all trials, the primary outcome was impact on amount of menstrual blood loss after 24 weeks. Secondary outcomes included quality of life, measured through the UFS-QoL questionnaire, amenorrhoea rates, serum haemoglobin levels, fibroid/uterine volume and pain scores. Adverse effects were studied, including loss of BMD, hot flashes, headache, changes in liver transaminases, lipid levels and endometrium. These outcomes were assessed after a treatment period of 24 weeks. For the effects of continued treatment, open-label extension studies were performed for another 24–28 weeks

(total of 52-weeks treatment) for the relugolix-ABT and elagolix-ABT. Impact on fertility or pregnancy outcomes was not evaluated. The elagolix-ABT extension trial reported on uterine/fibroid volume and BMD at 6 months, as well as the mean blood loss of the first menses, after treatment cessation.[20] For the linzagolix trials, it has been indicated that a 24-week off-treatment report will follow in a separate manuscript.[19]

4.3 | Ad 3. Comparison to the standard of care

Guidelines provide an overview of established long-term treatment options for symptomatic fibroids, with pharmaceutical options such as tranexamic acid with or without a nonsteroidal anti-inflammatory drug, oral combined contraceptives or progesterone-only options. Non-pharmacological options include hysterectomy, myomectomy (per abdomen or transcervical) and uterine artery embolization.[29–31] Given the relatively broad spectrum of fibroid symptoms, the most suitable comparison for effect of a novel treatment option is dependent on the main symptom and aim of the treatment.

To date, oral GnRH antagonist combination therapies, intended for longer term use, have not been compared to other treatment options. A prospective cohort study of myomectomy *vs* uterine artery embolization *vs* oral GnRHant-ABT is the only comparative study registered at ClinicalTrials.gov, for which recruitment has not yet started.[32]

4.4 | Ad 4. Long-term safety outcomes

For fibroid treatments long-term safety entails both direct as well as indirect adverse effects. Direct adverse effects of pharmacological treatment include headache, nausea, hot flushes, effects on renal, lipid and liver parameters, BMD, cardiovascular and thromboembolic risk profile, as well as contraceptive reliability, and, in case of unplanned pregnancy, teratogenicity. For surgical treatments, perioperative complications form a direct adverse effect. Indirect adverse effects can be post treatment risks such as uterine scar dehiscence during pregnancy or labour after abdominal myomectomy, or the effect on fertility through ovarian reserve or the time to resumption of a normal cycle.

From all trials, evaluations encompassed relevant safety outcomes, which were limited to direct effects. There have been no safety issues reported in the phase 1, 2 or 3 trials. The maximum duration of safety evaluation has been 52 weeks. Liver and lipid spectrum parameters remained stable with continued use. Hypoestrogenic side effects such as hot flushes, as well as BMD loss have been assessed in all trials after a 24-week treatment period, as well as in the extension trials reporting after a 52-week treatment period. In the relugolix-ABT and elagolix-ABT trials, these outcomes were assessed in a selected group of participants (see Ad 1.), and without a comparative placebo group. For the linzagolix trials, selection criteria were not provided.[16,19,20]

None of the trials reported a venous or arterial thromboembolic event. While long-term cardiovascular and thromboembolic risk profiles are still unknown, ABT is contraindicated for patients with a history of or current thromboembolic or cerebrovascular event. There is limited data on the effect of oral GnRHant during pregnancy. When exposed early in pregnancy, there may be increased risks of pregnancy loss. Teratogenicity has only been studied in rabbit and rat-models where no fetal malformations were reported.[12,16,33] Ongoing collection on long-term safety through trials has yet to be commenced. A real-world study with elagolix-ABT has terminated recruitment for not specified strategic reasons after 23 of the planned 200 inclusions in August 2022.[34] Another long-term safety study, also with elagolix-ABT, has been reported on clinicaltrials.gov since September 2017, but recruitment has yet to be commenced.[35] For relugolix-ABT, an open-label clinical interventional trial started in March 2021 to assess its contraceptive efficacy in women with either symptomatic fibroids or endometriosis, with final inclusion of 1020 women and completion expected in April 2025.[36]

5 | DISCUSSION

Three new oral GnRH antagonists with ABT have been authorized for either the 'management of heavy menstrual bleeding associated with uterine leiomyomas' or 'treatment of moderate to severe symptoms of uterine fibroids'.[12–15] These are Myfembree® and Ryeqo® (both with relugolix), Oriahnn® (with elagolix), and Yselty® (with linzagolix). Authorizations were based largely on randomized, double-blinded, placebo-controlled trials. In populations of premenopausal women with an average fibroid diameter of less than 5 cm, menstrual blood loss of 225 mL and moderate symptom severity, good effects on menstrual blood loss and quality of life scores at 24 weeks were reported. No robust and clinically significant reduction in fibroid volume was found. These outcomes were evaluated after a 24-week treatment period and, in the extension trials, a 52-week treatment period.

With regulatory approval for new treatments, practitioners should be cognizant of the trial findings and the populations that were studied. In this way, they can carefully consider the applicability of trial data to their individual patients. This is particularly germane to uterine fibroids which are not only highly prevalent but affect women of all ages and races, present in a variety of sizes, numbers and uterine locations and cause a variety of clinical symptoms. However, product information generally does not provide enough information to inform clinicians adequately. Although robust effects on the reduction of heavy menstrual blood loss and improvement in QoL scores were reported in all trials, generalizability to the broad population of women encountered in clinical practice is limited. While a diverse range in age and BMI were found in all trials, racial representation was narrower. Black women were included in large numbers in all but one of the trials whereas participants of Asian descent were lacking. Although the prevalence as well as the burden of symptoms of fibroids is known to be higher in Black women compared to White women,[23] women of East Asian descent are also known to have

increased fibroid burden compared to White women and so it is important that this racial group of women be studied.[37,38] In a community-based cross-sectional study including 996 participants of reproductive age, fibroid prevalence was 21.8% in Asian-Chinese participants, 35.75% in Black or African-American participants, compared to 10.7% in White participants.[37]

To understand which kind of fibroids are most suitable for treatment with GnRHant-ABT, transparency on the distribution of fibroid characteristics amongst trial participants such as size, FIGO type (location) and number is needed because such fibroid characteristics will impact symptomatology and prognosis.[39] The currently available trial data do not provide this more detailed, but highly clinical-relevant information, thereby restricting the predictability of expected efficacy and effectiveness in the more heterogeneous, real-world population. Regarding fibroid(s)/uterine size, we can deduce from the trial baseline characteristics that the majority of participants had fibroids smaller than 5 cm in diameter. The uteri were of moderate size of around 400 cm^3, corresponding to approximate uterine measurements of $14 \times 7 \times 8$ cm (ellipsoid volume formula). It should be noted that two of the registration trials excluded participants with significantly large uteri. In addition to understanding the moderate size of uteri and fibroids in the reported trials, the main fibroid-related symptom(s) need to be appreciated if we are to individualize management. Managing patients with symptomatic fibroids necessitates an understanding of the presenting symptoms, namely heavy menstrual blood loss, bulk pressure effects and reproductive failure. For example, if blood loss as opposed to bulk symptoms are the main complaint, then any tolerable medical treatment resulting in blood loss reduction without reducing uterine volume can yield good results.

It should be noted that it is possible that women with more severe symptoms were excluded from trial participation since all trials excluded women with significant anaemia (Hb < 8 g/dL (5 mmol/L) for the relugolix and elagolix ABT trials, <6 g/dL (3.7 mmol/L) for the linzagolix-ABT trials) and two registration trials excluded women who were likely to require surgery in the near future. Effectiveness in these patient groups is thus still unknown. While it has been suggested that GnRHant-ABT will reduce surgical procedures,[40,41] such conclusions cannot be drawn from the current evidence. There is a lack of comparison with current standard treatments. Prior to implementation of a new treatment option into clinical practice, this would ideally be performed in randomized clinical trials to assess (non-)inferiority and assure comparable patient populations, specifically when it concerns uterine-sparing treatments.[24.] To date, one prospective cohort study has been registered to assess the change in menstrual blood loss comparing treatment with elagolix-ABT, myomectomy and embolization. Recruitment has not yet commenced.[42]

Several other important issues need addressing. Firstly, there is a lack of clinically meaningful and consistent fibroid and uterine volume reduction. The only statistically significant and consistent (i.e. reported by both trials within one study) volume changes were seen with the treatment of relugolix-ABT and linzagolix 100 mg monotherapy, where uterine volume reductions of up to 14%–17% were reported. The latter would translate into an average diameter decrease from 8.6 to 8.1 cm. While no consistent fibroid volume reductions were found, the uterine volume reduction could imply a reduced fibroid load. However, it is unlikely that these small reductions are clinically meaningful. Results, moreover, indicate that no further reductions are found with continued treatment after 24 weeks. Given the limited volume reduction during prolonged treatment with oral GnRHant-ABT, it is expected that symptom severity outcomes specifically related to bulk pressure symptoms will not improve. High-dose GnRHant monotherapy does provide clinically meaningful and consistent fibroid as well as uterine volume reduction, as seen with linzagolix 200 mg.[19] However, as this preparation is registered only for treatment of up to 6 months, it will only provide a temporary volume reduction. It could therefore be further assessed as a possible presurgical treatment option.

Secondly, oral GnRHant-ABT treatment only provides symptom reduction during treatment. Importantly, the first menses after cessation of elagolix-ABT was within 2 months for 79% of women and was heavy with a reported mean volume of 199 mL.[20] It is therefore necessary to continue oral GnRHant treatment either until menopause or until a non-pharmaceutical treatment has been completed. Patients must be made aware of this by physicians during counselling and shared decision making, especially in light of the FDA's advice to limit treatment to 24 months.[12,13] Information on sustained effects of continued treatment beyond 52 weeks is lacking. In the majority of the trials, only half of the initially treated patients completed the extended 52-week treatment period, while two of the three registration trials excluded nonresponders after 24 weeks of treatment. The number of women requiring surgical interventions in the long run is also uncertain from the available trial data.

Thirdly, it is important to address the possible desensitization effect. In contrast to GnRH agonists, the antagonists competitively block receptors resulting in a sensitization of endogenous receptors.[43] This sensitization could result in a rebound effect, as seen by an accelerated growth of fibroid and uterine volume after cessation of GnRHant-ABT treatment, and likely a worsening of symptoms in the long run. Results published in the supplementary material of the elagolix-ABT extension trial may suggest such mechanisms, where uterine fibroids were shown to quickly return to a state of growth after treatment cessation, and at 6-months post treatment grow beyond the baseline value. While the first menses after cessation of elagolix-ABT was reported to be heavy, the effect on menstruation beyond the initial cycle is unknown.[20]

Furthermore, fibroids can affect fertility and pregnancy outcomes. The registration trials have not assessed either of these outcomes for long-term GnRHant-ABT treatment, whereas having a long-term wish to conceive, after treatment cessation, is no contraindication. The delicacy of the pregnancy-related questions in relation to symptomatic fibroids demands robust evidence on the effect of a new treatment on these outcomes before it is actually applied in this group of patients, which forms a challenge even for the already established fibroid treatment options. However, even if gathering robust evidence for reproductive outcomes proves to be very challenging, this should nevertheless be undertaken, specifically with novel molecular entities

for therapy of uterine fibroids. A prospective real-world data cohort of GnRHant-ABT could provide insight into this clinically meaningful outcome; to our knowledge, none is currently held. Negative impact of fibroids on reproductive outcomes is thought to relate to distortion of the endometrial contour, the uterine cavity as well as tubal ostia.[44] From this perspective, primary treatment for fibroids where retaining fertility potential is important should ideally be aimed at volume reduction. Perhaps post myomectomy treatment with GnRHant-ABT could play a role in providing a status quo for women not yet able to actively try to conceive. Currently a randomized open-label trial is recruiting participants to assesses fibroid recurrence at 24 months after myomectomy comparing postsurgical relugolix-ABT treatment to no intervention.[45] Moreover, observational trials have started recruitment evaluating the contraceptive efficacy of relugolix-ABT and the effect on pregnancy outcomes in terms of congenital malformations.[46,47]

Finally, several long-term safety issues need to be considered. The rapid implementation of ulipristal and the issues concerning liver problems taught us the importance of good long-term safety monitoring.[48,49] As with all new pharmaceutical treatments, long-term clinical as well as safety data is not yet available. While in the UK, Europe and Australia, a DEXA scan after 1 year is advised, and no limit to treatment duration is provided,[16,33,50,51] the FDA advises a treatment duration of up to 24 months, due to the risk of continued BMD loss which may not be reversible.[12,13] Although small reductions in BMD of 1%–2% were reported with GnRHant-ABT preparations after a 1-year treatment, there is a caveat. For reference, BMD loss of 6%–12% with the first year of glucocorticoid use[52] and up to 5% with pregnancy have been observed.[53] However, data provided from the oral GnRHant extension trials, which excluded women with BMD loss of >7%–8% after 24 weeks of treatment in the relugolix and elagolix trials, indicate that BMD does not stabilize, but reduces further with continued treatment of up to 52 weeks. The effect on BMD beyond this treatment period is still unknown. Currently, a study evaluating long-term safety in terms of BMD is underway, with the first year being double-blinded followed by 3 years of open-label treatment with elagolix-ABT. This trial is active, yet not recruiting.[54]

Both in the UK as well as in the US, oral GnRHant-ABT treatment has been added to the guidelines as treatment option for symptomatic fibroids.[29,31] As seen after the marketing authorization of ulipristal, even without comparative evidence, due to the great demand for an effective pharmaceutical treatment of symptomatic fibroids, uptake in clinical practice can be swift.[55] However, in light of the abovementioned issues, treatment of GnRHant-ABT would be most suitable for women who wish to reduce heavy menstrual bleeding temporarily (e.g. bridging up until surgery) or for women who are nearing menopause. In addition, the suggestion that GnRhant-ABT could 'prevent surgery' or provide an 'alternative to surgery' is not applicable to the majority of women that are not close to menopause. Labelling the treatment indication as 'treatment of moderate to severe symptoms due to uterine fibroids' (Europe, UK and Australia)[14,15,50,51] is, in our view, too broad. We believe a more precise labelling that reflects the studied population and the efficacy outcomes, will prevent unnecessary costs and unwarranted prescriptions before widespread implementation in clinics occurs, as we have seen in the treatment with ulipristal.[55]

6 | CONCLUSION

Six large, well-conducted double-blind randomized placebo-controlled trials have shown that oral GnRHant-ABT are efficacious in the treatment of heavy menstrual blood loss in women with fibroids when compared to placebo. The lack of clarity in distribution of fibroid characteristics in the trials, however, restricts the predictability of expected efficacy and effectiveness in the real-world heterogeneous population. No clinically meaningful fibroid and uterine volume reductions were observed for long-term GnRHant treatment. Only relugolix-ABT and linzagolix 100-mg monotherapy had significant, yet clinically debatable small uterine volume reductions. Moreover, a return of heavy menstrual blood loss and fibroid growth occurred swiftly after cessation of treatment, indicating that this treatment postpones symptoms without a lasting effect, thus should be used until menopause. With regard to safety and adverse events, short-term outcomes appear to be favourable in terms of BMD changes, and lipid as well as liver levels. However, there is a need for careful consideration of these factors when evaluating the overall safety of the treatment, particularly with long-term prescriptions. Real-world data on GnRHant-ABT should ideally be monitored, enabling improved future patient selection and possibly preventing premature cessation of a much sought-after uterine-sparing fibroid treatment. Equally urgent is the need for head-to-head comparison with current standard of fibroid care, through randomized clinical trials, in order to aid clinical and shared decision making. Oral combined GnRH antagonist with add-back therapy could potentially bring us one step closer to a much desired, effective, safe, noninvasive long-term treatment option for symptomatic fibroids in women. Yet current evidence does not provide enough base for broad implementation, nor can it be regarded as a comparable alternative to current nonmedical treatment options.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[56]

AUTHOR CONTRIBUTIONS

Maria E. de Lange, Annika Semmler, Judith A. F. Huirne and Wouter J. K. Hehenkamp were responsible for the conceptualization of this manuscript. T. Justin Clark, Ben Willem J. Mol and Pierre M. Bet made substantial contributors to the writing of the manuscript. Maria E. de Lange, Annika Semmler and Wouter J. K. Hehenkamp were

responsible for the original draft, but this was extensively reviewed and critically revised by all authors to clarify all sides of this review. All authors approved the final version of this manuscript and agreed that they are accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

T.J.C. declares to have received honoraria from Gedeon Richter, the manufacturer of Ryeqo (an oral GnHR antagonist combination therapy for the treatment of symptomatic fibroid) for a lecture (webinar) in 2022 on the management of fibroids. B.W.J.M. declares to have received an investigator grant (GNT1176437) from NHMRC; to have received consulting fees from ObsEva, Merck KGaA and Guerbet at an hourly rate; to have received travel support from Merck KGaA. J.A.F.H. declares to have received research grants from NOW-ZonMw/TTW and Samsung on topics not related to the manuscript topic; to have received compensation for expenses made to give an annual course on minimal invasive surgery and for a lecture on imaging on a sponsored session at an international congress. M.D.L, A.S., P.M.B. and W.J.K.H. declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

ORCID

Maria E. de Lange https://orcid.org/0000-0001-5953-6270

REFERENCES

1. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. *BJOG*. 2017;124(10):1501-1512.
2. Donnez J, Dolmans MM. Uterine fibroid management: from the present to the future. *Hum Reprod Update*. 2016;22(6):665-686.
3. Stewart EA, Laughlin-Tommaso SK, Catherino WH, Lalitkumar S, Gupta D, Vollenhoven B. Uterine fibroids. *Nat Rev Dis Primers*. 2016;2:16043.
4. de Lange ME, Huirne JAF. Linzagolix: an oral gonadotropin-releasing hormone receptor antagonist treatment for uterine fibroid-associated heavy menstrual bleeding. *Lancet*. 2022;400(10356):866-867.
5. Tukun FL, Olberg DE, Riss PJ, Haraldsen I, Kaass A, Klaveness J. Recent development of non-peptide GnRH antagonists. *Molecules*. 2017;22(12):2188.
6. Boyce M, Clark E, Johnston A, George M, Davies J, Hibberd M. Effects of single and repeated oral doses of TAK-013, a new non-peptide gonadotropin-releasing hormone (GnRH) antagonist, in healthy post-menopausal women. *Fertil Steril*. 2002;78:S281-S282.
7. Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med*. 2020;382(23):2187-2196.
8. MacLean DB, Shi H, Faessel HM, Saad F. Medical castration using the investigational oral GnRH antagonist TAK-385 (relugolix): phase 1 study in healthy males. *J Clin Endocrinol Metab*. 2015;100(12):4579-4587.
9. Diamond MP, Carr B, Dmowski WP, et al. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. *Reprod Sci*. 2014;21(3):363-371.
10. Huirne JAF, Lambalk CB. Gonadotropin-releasing-hormone-receptor antagonists. *Lancet*. 2001;358(9295):1793-1803.
11. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. *J Clin Endocrinol Metab*. 2017;102(5):1683-1691.
12. AbbVie. ORIAHNN: Highlights of prescribing information 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213388s000lbl.pdf. Accessed September 11, 2023.
13. MyovantSciences. MYFEMBREE: Highlights of prescribing information. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214846s000lbl.pdf. Accessed September 11, 2023.
14. GedeonRichter. Ryeqo: Summary of Product Characteristics 2021. https://www.ema.europa.eu/en/documents/product-information/ryeqo-epar-product-information_en.pdf. Accessed September 11, 2023.
15. ObsEva. Yselty: Summary of Product Characteristics 2022. https://www.ema.europa.eu/en/documents/product-information/yselty-epar-product-information_en.pdf. Accessed September 11, 2023.
16. EMA. Ryeqo: EPAR—Public assessment report 2021. https://www.ema.europa.eu/en/documents/assessment-report/ryeqo-epar-public-assessment-report_en.pdf. Accessed September 11, 2023.
17. Al-Hendy A, Lukes AS, Poindexter AN 3rd, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. *N Engl J Med*. 2021;384(7):630-642.
18. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med*. 2020;382(4):328-340.
19. Donnez J, Taylor HS, Stewart EA, et al. Linzagolix with and without hormonal add-back therapy for the treatment of symptomatic uterine fibroids: two randomised, placebo-controlled, phase 3 trials. *Lancet*. 2022;400(10356):896-907.
20. Simon JA, Al-Hendy A, Archer DF, et al. Elagolix treatment for up to 12 months in women with heavy menstrual bleeding and uterine leiomyomas. *Obstet Gynecol*. 2020;135(6):1313-1326.
21. Al-Hendy A, Lukes AS, Poindexter A III, et al. Liberty: long-term extension study demonstrating one-year efficacy and safety of relugolix combination therapy in women with symptomatic uterine fibroids. *Fertil Steril*. 2020;114(3):e1.
22. EMA. *From laboratory to patient: the journey of a centrally authorised medicine*. European Medicines Agency; 2019. Accessed September 11, 2023. https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf
23. Eltoukhi HM, Modi MN, Weston M, Armstrong AY, Stewart EA. The health disparities of uterine fibroid tumors for African American women: a public health issue. *Am J Obstet Gynecol*. 2014;210(3):194-199.
24. Stewart EA. Comparing apples to apples for fibroids. *N Engl J Med*. 2020;383(5):489-490.
25. Stewart EA, Nicholson WK, Bradley L, Borah BJ. The burden of uterine fibroids for African-American women: results of a national survey. *J Womens Health (Larchmt)*. 2013;22(10):807-816.
26. Magnay JL, Schönicke G, Nevatte TM, O'Brien S, Junge W. Validation of a rapid alkaline hematin technique to measure menstrual blood loss on feminine towels containing superabsorbent polymers. *Fertil Steril*. 2011;96(2):394-398.
27. Spies JB, Coyne K, Guaou Guaou N, Boyle D, Skyrnarz-Murphy K, Gonzalves SM. The UFS-QOL, a new disease-specific symptom and health-related quality of life questionnaire for leiomyomata. *Obstetr Gynecol*. 2002;99(2):290-300.
28. Hervé F, Katty A, Isabelle Q, Céline S. Impact of uterine fibroids on quality of life: a national cross-sectional survey. *Eur J Obstet Gynecol Reprod Biol*. 2018;229:32-37.
29. NICE. Heavy menstrual bleeding: assessment and management (NICE Guideline NG88) 2018. Accessed September 11, 2023. https://www.nice.org.uk/guidance/ng88
30. NVOG. Hevig menstrueel bloedverlies (HMB) 2021. Accessed September 11, 2023. https://richtlijnendatabase.nl/richtlijn/hevig_menstrueel_bloedverlies/hevig_menstrueel_bloedverlies_-_startpagina.html

31. ACOG. Management of symptomatic uterine leiomyomas. ACOG practice bulletin no. 228. *Obstet Gynecol*. 2021;137(6):e100-e115. doi:10.1097/AOG.0000000000004401
32. National Library of Medicine. Myomectomy vs Uterine Artery Embolization vs GnRh Antagonist for AUB-L (Magical). Identifier: NCT04856306. 2021 April—[updated May 5, 2022]. Accessed September 11, 2023. https://clinicaltrials.gov/ct2/show/NCT04856306
33. EMA. Yselty: EPA—Public assessment report 2022. Accessed September 11, 2023. https://www.ema.europa.eu/en/documents/assessment-report/yselty-epar-public-assessment-report_en.pdf
34. National Library of Medicine. A Study to Assess Patient-Reported Quality of Life and Effectiveness on Control of Bleeding in Adult Participants With Heavy Menstrual Bleeding Due to Uterine Fibroids Taking Oral Oriahnn Capsules (REACH). Identifier: NCT05026502. October 5, 2021–August 30, 2022. Accessed September 11, 2023. https://clinicaltrials.gov/ct2/show/NCT05026502
35. National Library of Medicine. Long-Term Safety Study of Elagolix in Combination With Estradiol/Norethindrone Acetate for the Management of Heavy Menstrual Bleeding Associated With Uterine Fibroids in Premenopausal Women. Identifier: NCT03271489 2017, September. Accessed September 11, 2023. https://clinicaltrials.gov/ct2/show/NCT03271489
36. National Library of Medicine. Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women With Uterine Fibroids or Endometriosis Who Are at Risk for Pregnancy (SERENE). Identifier: NCT04756-37. 2021, March. Accessed September 11, 2023. https://clinicaltrials.gov/ct2/show/NCT04756037
37. Huang D, Magaoay B, Rosen MP, Cedars MI. Presence of fibroids on transvaginal ultrasonography in a community-based, diverse cohort of 996 reproductive-age female participants. *JAMA Netw Open*. 2023;6(5):e2312701.
38. Murji A, Bedaiwy M, Singh SS, Bougie O. Influence of ethnicity on clinical presentation and quality of life in women with uterine fibroids: results from a prospective observational registry. *J Obstet Gynaecol Can*. 2020;42(6):726-733.
39. Dolmans MM, Cacciottola L, Donnez J. Conservative management of uterine fibroid-related heavy menstrual bleeding and infertility: time for a deeper mechanistic understanding and an individualized approach. *J Clin Med*. 2021;10(19):4389. doi:10.3390/jcm10194389
40. Roberts M. Offer women oral tablet to treat fibroids, NHS advised. BBC News May 13, 2022. Accessed September 11, 2023. https://www.bbc.com/news/health-61426099
41. Al-Hendy A, Bradley L, Owens CD, et al. Predictors of response for elagolix with add-back therapy in women with heavy menstrual bleeding associated with uterine fibroids. *Am J Obstet Gynecol*. 2021;224(1):1-50.
42. National Library of Medicine. Myomectomy vs Uterine Artery Embolization vs GnRh Antagonist for AUB-L (Magical). NCT04856306. April 12, 2021–June 30, 2025. Accessed September 11, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04856306
43. Banga FR, Huirne JA, Korsen T, Homburg R, Hompes PG, Lambalk CB. Pituitary sensitizing effect of GnRH antagonists: a mechanism explaining LH escape during IVF? *Hum Reprod*. 2010;25(6):1513-1519.
44. Myomas and reproductive function. *Fertil Steril*. 2008;90(5 Suppl):S125-S130.
45. National Libarary of Medicine. Surgical Myomectomy Followed by Oral Myfembree versus Standard of Care Trial (SOUL). NCT05538689. November 20, 2022–April 2026. Accessed September 11, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05538689
46. National Libaray of Medicine. Study of the Safety and Contraceptive Efficacy of Relugolix Combination Therapy in Women With Uterine Fibroids or Endometriosis Who Are at Risk for Pregnancy (SERENE). NCT04756037 March 18, 2021–April 2025. Accessed September 11, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04756037
47. National Library of Medicine. Relugolix Pregnancy Registry: an Observational Study of the Safety of Relugolix-Containing Therapy Exposure in Pregnant Women and their Offspring NCT05739123. (May 8, 2023–). Accessed September 11, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT05739123
48. Middelkoop MA, Bet PM, Drenth JPH, Huirne JAF, Hehenkamp WJK. Risk–efficacy balance of ulipristal acetate compared to surgical alternatives. *Br J Clin Pharmacol*. 2021;87(7):2685-2697.
49. Middelkoop MA, Harmsen MJ, Manyonda I, et al. Uterine artery embolization versus surgical treatment in patients with symptomatic uterine fibroids: protocol for a systematic review and meta-analysis of individual participant data. *Eur J Obstet Gynecol Reprod Biol*. 2021;256:179-183.
50. GedeonRichter. Australian Product Information Ryeqo 2022. Accessed September 11, 2023. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2022-PI-01955-1&d=20221102172310101
51. GedeonRichter. Ryeqo 40 mg/1mg/0.5mg film-coated tablets 2021. Accessed September 11, 2023. https://www.medicines.org.uk/emc/product/12934/smpc#gref
52. Chotiyarnwong P, McCloskey EV. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. *Nat Rev Endocrinol*. 2020;16(8):437-447.
53. Winter EM, Ireland A, Butterfield NC, et al. Pregnancy and lactation, a challenge for the skeleton. *Endocr Connect*. 2020;9(6):R143-R157.
54. National Library of Medicine. Long-term safety study of Elagolix in combination with estradiol/norethindrone acetate for the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women. NCT03271489. September 13, 2017–July 2, 2024. Accessed September 11, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT03271489
55. Middelkoop M-A, de Lange ME, Clark TJ, et al. Evaluation of marketing authorization and clinical implementation of ulipristal acetate for uterine fibroids. *Hum Reprod*. 2022;37(5):884-894.
56. Alexander SPH, Christopoulos A, Davenport AP, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. *Br J Pharmacol*. 2019;176(S1):S21-S141.

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